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ACTINOMYCOSIS OF THE OVARIES AND FALLOPIAN TUBES*

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ACTINOMYCOSIS of the ovaries and Fallopian tubes is one of the less common diseases confronting the gynecologist. Since, however, there are more than one hundred reports of cases of this condition in the literature, every gynecologist who treats so-called pelvic inflammatory disease should be aware of the possibility of infection with Actinomyces.

In the past, the outcome of this disease when it affects the female internal genitals has not been encouraging. The advent of chemotherapy has markedly changed the prognosis. There have been no extensive studies of the problem since sulfonamide compounds and penicillin came into general use. Hence, it was thought that a comprehensive study would be of benefit to those who are likely to be confronted with pelvic actinomycosis.

Antecedent Studies

According to Gardiner and Welsh, the credit for the discovery of Actinomyces goes to Laugenbeck, who found "sulfur granules" in the jaw lesions of cattle in 1845. According to Wright, Harz in 1877 suggested the name "ray fungus" or "Actinomyces bovis."

Rosebury[36] stated that Wolff and Israel in 1891 were the first to obtain pure cultures of the organism.

Numerous cases of actinomycosis were reported by 1905, but there were few concerning the internal female genitals. In 1909 Taylor and Fisher found only six cases. In 1919 Robinson could find only nineteen cases of actinomycosis of

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the Fallopian tubes and ovaries. Helwig reported thirty cases in 1925. In 1934 the number had risen to seventy-two, as reported by Cornell. We found thirty-seven more cases in the literature up to 1946. These have been added to this study, bringing the total to one hundred nine.

Materials and Methods, Present Study

This study is based on the literature and on eight cases from the files of the Mayo Clinic. A summary has been made of all cases reported up to Jan. 1, 1946. Our eight cases are reported in detail, with special reference to the pathology, treatment, and prognosis.

The statistical results compiled in a study of the cases in the literature and of our cases are analyzed separately and compared. Emphasis is placed on the diagnostic and therapeutic measures used in this disease to show how they have changed in the past decade.

Pathogenesis

The causative organism of actinomycosis is a delicate, thermolabile, anaerobic fungus which has been given the name *Actinomyces bovis*. This is the organism of Wolff and Israel, and its specificity has been definitely proved. *Actinomyces bovis* also causes lumpy jaw in cattle. Actinomycosis is found the world over; there is no evidence of endemicity. In the United States, Sanford found the disease especially prevalent in the upper Mississippi River valley and the northwest region.

In 80 per cent of cases the disease occurs in young adult persons. Occupation seems to have no influence on it. Macnab wrote that there is little evidence that the disease can be transmitted directly from man to animal or from animal to man. Contagion from man to man never has been established.

There are two views as to the mode of entry of the organism:

Exogenous Route.—Supporters of this theory cite the cases in which a history of the chewing of raw grain or grasses has been elicited. There are also cases in which barbs of grain have been found in the actinomycotic lesions. These factors constitute circumstantial evidence that the chewing of grasses and grains may predispose the victim to the disease.

Endogenous Route.—The bulk of evidence indicates that Actinomyces are normal inhabitants of the mouth and intestinal tract. Slack isolated anaerobic Actinomyces from fourteen of one hundred tonsils removed consecutively, and from eighteen of one hundred samples of pus from persons with pyorrhea. Emmons found Actinomyces-bearing granules in forty-seven of one hundred pairs of tonsils. Weller found eight instances of tonsillar concretions in 1,000 tonsils; forty-seven of these eighty were composed of Actinomyces-like colonies of mixed organisms.

The organism is an anaerobic fungus, difficult to grow. It has not been isolated from grasses and grains. It probably cannot invade tissue except under favorable circumstances. Minor trauma is thought to be necessary to give the organism a portal of entry.

Portal of Entry in Actinomycosis of Fallopian Tubes and Ovaries.—The intestinal tract probably is the prime seat of infection. In most cases the disease is thought to have this origin, even though a lesion in the bowel is demonstrated rarely. Failure to demonstrate a macroscopic or a microscopic lesion in the intestine adjacent to the ovarian mass has been variously explained. First, Brickner felt that the organism could pass through the gut wall without producing a lesion therein. Second, it may be that there is a primary lesion in the wall of the bowel, but if so, such a lesion might be healed by the time the disease is manifest in the tubes and ovaries, since mucous membrane is known to

be resistant to Actinomyces. Third, the disease may be spread by the help of other organisms. Fourth, it may be spread by the blood stream.

Gardiner and Welsh believed the ovaries are the chief sites of pelvic infection with this disease. The proximity of the right ovary to the appendix is said to be important, because the appendix is the commonest site of abdominal actinomycosis. The ovaries are thought to be favorable sites for the lodgment and growth of the organism, especially at the time of ovulation.

It is also possible for the organism to gain entry through the vagina. Tietze described a case in which the infection seemed definitely to follow the use of a pessary. De Faria and Fialho reported a case in which pelvic actinomycosis followed abortion attended by infection. Campbell and Greaves reported actinomycosis of the cervix uteri. Other authors[8, 15, 18, 20, 23, 29, 33, 34] have reported cases of actinomycosis that probably was primary in the pelvis.

The disease in the pelvis usually is restricted to the tubes and ovaries. The well-known resistance of the pelvic peritoneum and the tendency toward localization of infections in this area may account for the early seemingly benign course and protracted illness without more frequent evidence of early generalized peritonitis.

Bacteriologic Aspects

There has been much confusion in the literature regarding a system of classification of Actinomyces. The general classification of Waksman and Henrici is used in describing the fungi-producing true mycelia.

Actinomycetaceae.—These are organisms in which the mycelium fragments into bacillary or coccoid elements. These may be subdivided into Actinomyces and Nocardia.

Actinomyces.—Members of the genus Actinomyces are anaerobic or microaerophilic, parasitic, and not acid-fast. They are found in the alimentary tract of man and animals. They are gram-positive. In tissue they form "sulfur granules," which are cauliflower-shaped mycelial masses with radial-club arrangement at the periphery (Fig. 1, *a*). These clublike bodies (Fig. 1, *b*) are pear-shaped thickenings of the terminal filaments; they are hyaline, refringent, and vary in size and thickness. All transitions between the clubs and filaments may be present beneath the peripheral layer. On culture media they form bacteria-like colonies without aerial hyphae and they produce no spores or pigments. They grow best at body temperature. Their oxygen tolerance is very limited. They do not liquefy gelatin. The species is heterogenous and has not yet been satisfactorily subdivided. *Actinomyces bovis* or *Actinomyces israeli* is the best-known organism in this group. The term "actinomycosis" probably should be limited to lesions caused by this type.

Nocardia.—Members of the genus Nocardia are aerobic and partially acid-fast or are not acid-fast. They do not form spores. Species of Nocardia sometimes are pathogenic and may produce actinomycosis-like lesions in man.

Streptomycetaceae.—These are organisms in which the mycelium does not fragment. They are aerobic. They are found widely in nature in soils, manure, grasses, and grains. On culture, the colonies often produce aerial hyphae. They form highly specialized spores and various-colored pigments. These organisms grow best at 15° to 20° C. (59° to 68° F.). Many are actively proteolytic. They occasionally produce actinomycosis-like lesions in man. Streptomycetaceae may be divided into Streptomyces and Micromonospora.

Streptomyces.—Members of the genus Streptomyces multiply by the formation of conidia in chains from aerial hyphae.

Micromonospora.—Members of the genus Micromonospora multiply by the formation of single terminal spores on short sporophores.

Pathologic Aspects

Gross Pathologic Aspects.—As a rule, a granulomatous tubo-ovarian mass is seen adherent to surrounding structures. These masses vary from the size of a walnut to tumors filling the entire lower part of the abdomen. They are greenish white or yellowish, often mottled. They are soft, friable, fluctuant and

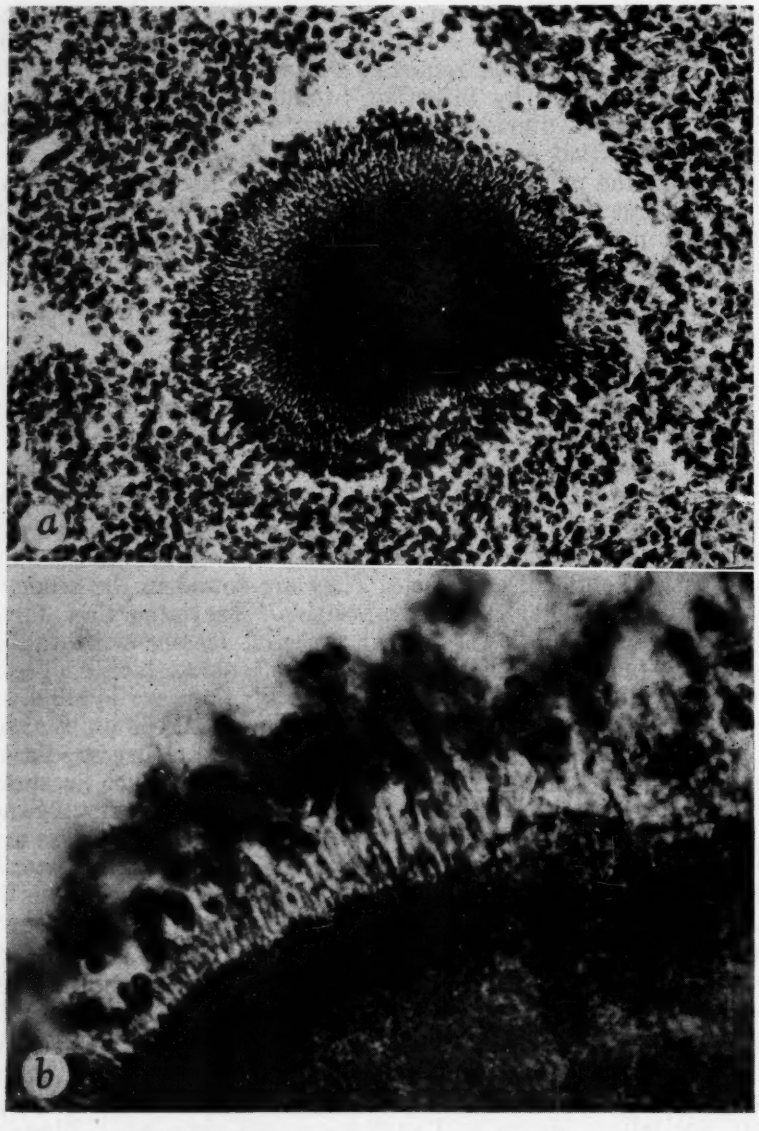

Fig. 1.—*a* (Case 7), Typical actinomycotic colony in section of an ovary (hematoxylin and eosin, ×240); *b* (Case 7), Detail of the peripheral club arrangement at the edge of a colony of actinomyces organisms (hematoxylin and eosin, ×900).

elastic, but occasionally may be hard. The surface may be smooth or roughened, but most often shows a moth-eaten appearance, with protrusions of various sizes and shapes. Pus may exude from the tumor.

On cross section, few or numerous, large and small, regular or irregular cavities are seen; these are filled with pus of varying color in a meshed network of milky-white to grayish black connective tissue. This gives the cut surface a cheesy, spongy, moth-eaten, or honeycomb appearance. As a rule, the pus is thick and slimy, and it varies in color and quantity. Granules of varying color and shade sometimes are found in the pus.

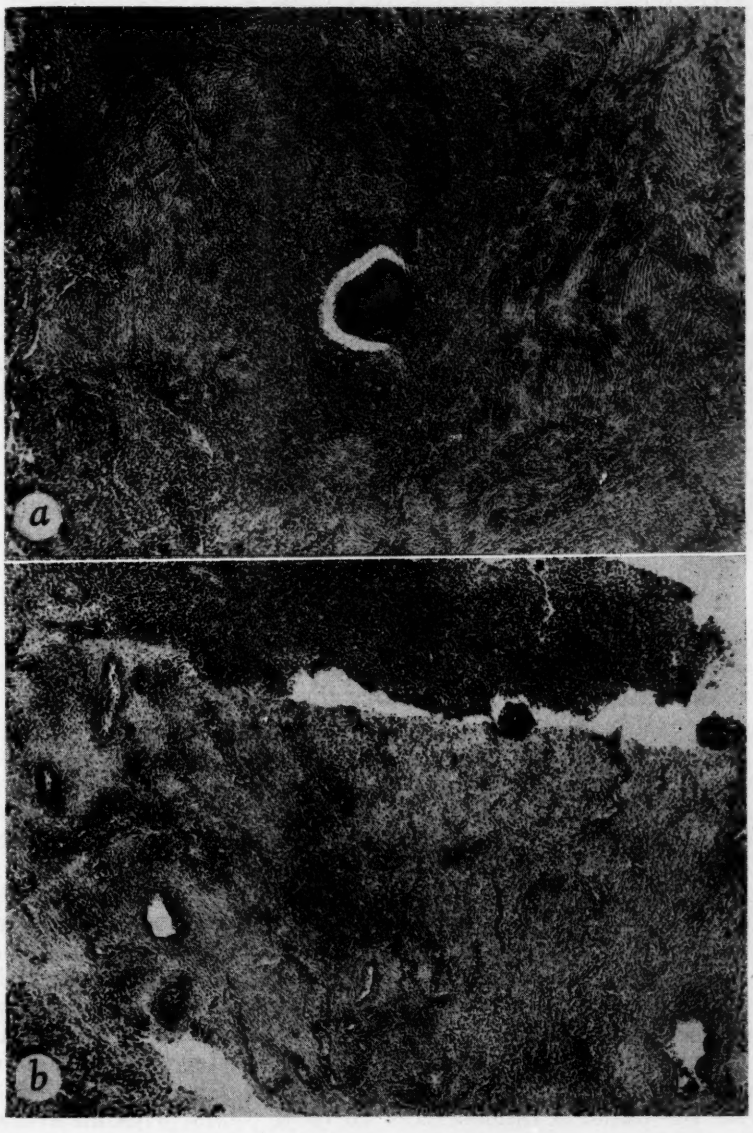

Fig. 2.—*a* (Case 7), Colony of actinomyces organisms in a small abscess surrounded by granulomatous fibroblastic stroma (hematoxylin and eosin, ×32); *b* (Case 8), A very small colony of actinomyces organisms (the only colony on this particular slide), showing normal character of the blood vessels in the granulomatous stroma (hematoxylin and eosin, ×32).

In some cases only the ovaries are involved; in others the Fallopian tubes also are invaded. Generally, there are inflammatory changes in the Fallopian tubes, even if no colonies of Actinomyces can be demonstrated. Infection of the

uterus itself is rare, but the parametrium often is involved. There may be sinus tracts into the bowel, bladder, or skin.

Microscopic Pathologic Aspects.—The lesions begin as an accumulation of polymorphonuclear leucocytes about the organism; this process eventually results in liquefaction necrosis (Fig. 1, *a*). About this center is a zone of lymphocytes and plasma cells, interspersing a mass of endothelial-like cells. This is surrounded by a loose honeycomb layer of granulation tissue and fibrosis. There is always a tremendous fibroblastic reaction (Fig. 2, *a*). The blood vessels in the fibroblastic stroma are intact in comparison with the endarteritis associated with tuberculous or syphilitic infections (Fig. 2, *b*). Caseation necrosis is not seen, but giant cells occasionally are observed. Calcification is rare. Under low-power magnification, multiple small abscesses of the type described above are seen (Fig. 2, *a*). Some of the areas of infection may show numerous colonies of organisms, but generally it is necessary to search for even a single colony. Other areas with the same microscopic appearance show no colonies.

Progress of the Lesions.—Actinomycosis spreads by direct extension or via the blood stream, rarely by the lymphatic route. The organism is said to be too large to be able to invade lymph channels. However, Draper and Studdiford reported one case in which the mesenteric lymph nodes were definitely involved with actinomycosis.

Usually, the lesions progress peripherally, producing adhesions to, and abscesses of, contiguous structures. These eventually rupture spontaneously to the surface, with the formation of sinuses. This process may be the body's attempt at extrusion of the infecting organism, as it would extrude a foreign body. The organism is capable of invading bone as easily as soft tissue; actinomycotic osteomyelitis is not uncommon. The free rupture of actinomycotic abscesses occasionally produces generalized peritonitis.

Clinical Course

Clinical Characteristics.—The early symptoms and course of actinomycosis of the internal female pelvic organs are not characteristic. In the early stages the disease simulates pelvic inflammatory disease of other causation, and, when it is more acute, it may resemble appendicitis. Seven of our eight patients gave a history of pain in the lower part of the abdomen, usually located on one side, at the onset of their illness. The remaining patient had had symptoms of partial obstruction of the bowel for which colostomy had been done. Six of the eight patients had associated fever; three experienced vomiting with their attacks. Only one patient (Case 3[6]) had noticed any swelling in the abdomen.

It is interesting to note that all eight patients had undergone surgical treatment elsewhere. In only one instance (Case 6) had actinomycosis been diagnosed prior to entry of the patients at the Mayo Clinic. Previous surgical treatment varied: six had undergone gynecologic operations; four of them had had some portion of the pelvic organs removed; one had undergone colpotomy; one had undergone a simple exploratory operation. Of the other two patients, one had undergone simple incision of an abdominal abscess; for the other, colostomy had been performed for partial obstruction of the bowel.

Ages of the patients ranged from 23 to 46 years, with an average of 34.4 years.

The duration of symptoms prior to entry of the patients varied from two to thirty-nine months, with an average of 17.7 months.

Five of the eight patients reported loss of weight. This finding was not commented upon in the records of the other three patients.

An abdominal mass was described in three of the cases. Six patients had draining sinuses, one of which was a draining wound after colpotomy. On pelvic

examination a mass was noted in seven of the eight cases. In the other case panhysterectomy had been done elsewhere, and results of the pelvic examinations were recorded as negative.

The laboratory findings in these eight cases were fairly consistent. The average erythrocyte count was 4,420,000 per c.mm. of blood; the average value for hemoglobin was 9.6 Gm. per 100 c.c. of blood. Six of the eight patients had an elevated leucocyte count; the elevation averaged 13,100 cells per c.mm. of blood. A sedimentation rate was calculated in five cases and found to be elevated in all five. The sedimentation rates (Westergren) varied from 30 to 127 mm. in one hour, with an average of 95.5 mm. in one hour. The urine of six of the eight patients contained pus and (or) albumin. In the other two cases results of urinalysis were negative.

The foregoing description of the records and findings shows little that can be called "typical of actinomycosis." In this series of eight cases, bacteriologic studies were made seven times. In five of these cases results of bacteriologic study were positive for Actinomyces and in the other two results were negative. These five positive results led to an early correct diagnosis.

Diagnosis.—The diagnosis of actinomycosis of the ovaries and Fallopian tubes usually is made on the basis of microscopic study of tissue removed at surgical operation or by culture. The early symptoms of pelvic pain, vomiting, and fever, and the early finding of a mass in the abdomen or pelvis do not ordinarily lead to a diagnosis of actinomycosis, because these signs are more often associated with pelvic inflammatory disease of other causation. The possibility of actinomycosis should be kept in mind when medical treatment fails, especially if the sedimentation rate remains high. The physicians who saw the eight patients in this series were in an unusually favorable position to make the correct diagnosis, since all the patients had undergone some operation before they came to the clinic and pus was available for study in six of the cases. In spite of this surgical treatment, the diagnosis had been established elsewhere in only one case (Case 6).

Five of the eight patients had draining sinuses on entry, and one had a draining colpotomy wound. Results of bacteriologic studies of pus from four of them were positive for Actinomyces.

Five of the eight patients underwent radical surgical treatment which made pathologic diagnosis possible. Colonies of Actinomyces were found microscopically in the specimens in four of these cases. The negative result occurred in Case 5, in which the patient had received eight months of intensive chemotherapy thirty months before operation. The diagnosis in this case had been established bacteriologically.

The colonies often are difficult to find with the microscope; repeated sections should be made when grossly the lesion is granulomatous and on section reveals multiple abscesses (Fig. 2, *b*). In Case 8 twenty-three sections were made from the abscessed areas at time of operation. Colonies of the organism were not found after careful study of sections. After this organism had been cultured from the pus, more sections were made from the tissue. Finally, two very tiny typical ray fungus colonies were located (Fig. 2, *b*). In Case 3 the diagnosis was not established until after necropsy, when the tissue removed at surgical operation was restudied for the possibility of Actinomyces.

In summary, the diagnosis in these eight cases was established either by culture (five times) or by microscopic study of sections of tissue (four times) or by both methods (once).

Treatment and Results.—The treatment of these eight patients was medical and surgical. When surgical treatment was employed, it was radical, with removal of all of the diseased tissue possible. Three of the eight patients were seen prior to the era of chemotherapy. Two of these, whose condition was diagnosed

by bacteriologic studies after extensive surgical treatment had been carried out elsewhere, were treated intensively with potassium iodide given by mouth, sodium iodide given intravenously. roentgen rays and radium. At the time of this writing, one of these was reported as being "cured" thirty-six months after treatment at the clinic; the other was reported as being "improved" two months after treatment at the clinic. The third patient in this group of three underwent salpingo-oophorectomy on the left and incision of an abscess in the left flank. This patient (Case 3) died on the twentieth postoperative day, from generalized peritonitis. The diagnosis in this case had not been established during the life of the patient.

The other five patients were seen after sulfonamide drugs and penicillin had become available. Four of these five were treated by radical surgical methods. The other patient (Case 6) was seen after extensive surgical treatment had been carried out elsewhere, and the disease had spread to the wall of the chest and the buttocks. She was treated with huge doses of penicillin, with marked regression of the actinomycotic lesions, but she died six weeks after her last visit to the clinic, when the disease became complicated by chronic glomerulonephritis. Of the four patients operated on, three received intensive chemotherapy postoperatively. In the fourth case the abscesses evidently had been sterilized by intensive preoperative therapy with sulfadiazine and penicillin. Two of these patients are reported as being "cured" thirty-three months and ten months, respectively, after treatment at the clinic. The other two were reported to be "improved" one month after operation.

In general, the dose of the sulfonamide drugs, when these were used, was standard for the patient's age and weight. Sulfadiazine was the drug of choice. Penicillin was administered in large doses, the usual course being 2,000,000 units given intravenously or intramuscularly daily for a period of ten days, and repeated as often as necessary to get the desired clinical results.

In summary, three of the eight patients were treated prior to the era of chemotherapy. Of these three, one was reported as "cured," one was "improved," and one died. Of the five patients who received sulfonamide drugs and (or) penicillin, two were reported as "cured," two as "improved" and one died. Three of the eight patients were not operated on; of these, one was reported as "cured," one as "improved," and one died. Of the five who received surgical treatment, two are reported as "cured," two as "improved" and one died. The totals for all eight patients are: three "cured," three "improved" and two dead.

Comment

It was felt, in respect to our cases as well as to those in the literature, that the chewing of grains and grasses, contact with animals, or contact with patients who had actinomycosis were not etiologic factors. It is generally accepted that the etiologic organism is *Actinomyces bovis*, although in our eight cases the clinician usually was satisfied with the report "sulfur granules found." This situation also was true in respect to the greater majority of cases reported in the literature. The upper Mississippi River valley area was the habitat of the eight patients involved in this series.

It was impossible to determine the mode of infection in any of the eight cases. Because of previous surgical operations, it could not be ascertained in which side the infection had originated, except in Case 8, in which at first only the left Fallopian tube and ovary were involved. From clinical study of our patients, it can be presumed that the infection was bilateral in five, in the left

adnexa in two, and in the right adnexa in one. In none was infection by way of the vagina and cervix suspected. Gardiner and Welsh wrote that the right ovary probably is the prime seat of pelvic actinomycotic infection. However, a summary of one hundred nine cases reported in the literature shows that the infection was bilateral in 44.4 per cent, on the right side in 37.8 per cent, and on the left in 17.8 per cent. Thus, in this respect, our cases differed little from those in the reports of other authors. It has to be assumed that the infection was endogenous and originated from some spot in the gastrointestinal tract.

The five available pathologic specimens in the eight cases exhibited the typical picture described uniformly in the literature. The Fallopian tubes and ovaries were the chief sites of the actual infection, although there were often inflammatory changes in the uterus and parametrium. In all five the pathologic picture was that of multiple granulomatous actinomycotic abscesses, with many dense and loose adhesions to surrounding structures and the frequent formation of sinus tracts.

The typical clinical history, as described in the literature, is that of a previously healthy woman who suddenly becomes ill with localized or diffuse lower abdominal pain, nausea, vomiting, and fever, or one who experiences gradual onset of symptoms referable to the pelvic organs, often with intermittent, more acute exacerbations. The menstrual periods may or may not be disturbed. Only occasionally does the patient detect a tumor mass, but frequently an operation for a pelvic tumor has been performed. In seven of our eight cases pain in the lower part of the abdomen was a prominent symptom. Six of the eight patients had fever, three had been nauseated and had vomited, and only one had noticed any swelling in the abdomen. All eight patients had undergone surgical operation elsewhere.

In the cases in the literature the ages of the patients ranged from fourteen to sixty-four years, with an average of 34.1 years. In the eight cases in the present series the range was twenty-three to forty-six years, with an average of 34.4 years.

The duration of symptoms in the cases in the literature varied from one month to 156 months, with an average of 19.4 months. The duration in the present series was two to thirty-nine months, with an average of 17.7 months.

In the usual case in the literature, loss of weight was reported, abdominal and (or) pelvic masses were described, anemia and leucocytosis were noted, and the sedimentation rate (when reported) was elevated. Of the eight patients reported on in this study, five had lost weight, seven had abdominal and (or) pelvic tumors, seven had hypochromic anemia, six had leucocytosis. Of five sedimentation rates reported in this series, all were elevated.

As can be seen from the foregoing, it is generally impossible to diagnose actinomycosis of the pelvic organs on the basis of the history and clinical findings. Serologic tests, agglutination tests, complement fixation reactions, and skin tests with culture filtrates have been tried, but render little help. The physician must be ever alert to suspect actinomycosis in cases of pelvic inflammatory disease which does not respond to medical or conservative surgical treat-

ment. The diagnosis is best made at time of operation, by microscopic examination of fresh tissue and (or) bacteriologic studies of the pus.

From a bacteriologic point of view, the diagnosis is easy when sulfur granules are found in pus from abscesses or sinuses. However, the granules are not always easy to find. They are described as yellow and sagolike to white and sandlike in appearance. They cannot be recognized grossly, and many things are mistaken for them: "pearls" of degenerated malignant tissue, small concretions or seeds from intestinal fistulas, small round masses of fibrin, masses of cocci, tuberculous debris, and crystals of iodoform. The pus should be strained through gauze and the granules obtained, soaked with strong sodium hydroxide on a glass slide, crushed, and stained by Gram's method. An alternative method is to embed the centrifuged sediment of pus in hard paraffin, make sections, and stain them with hematoxylin and eosin. Examination of the granules under the microscope usually will be conclusive. The disease may be advanced and suppurating many months before a search for the organism is rewarded. The organism may disappear from the pus after secondary infection has begun. Dorling[13] suggested that to obtain material for study, it is better to curet sinuses than to swab them. To add to the difficulty, Rosebury[36] wrote that *Actinomyces israeli* may fail to show clubs, and that similar if not identical clubs may be found in other disease processes, notably actinobacillosis.

Actinomyces is difficult to isolate and culture, which not only makes the diagnosis difficult but also gives trouble in testing for the sensitivity of the organism to drugs such as penicillin. Greenblatt and Gleenblatt stressed the importance of routine anaerobic as well as aerobic culture techniques and recommended media containing sulfhydryl compounds. In the eight cases in this study, bacteriologic studies were made seven times and results were positive five times.

Pathologic diagnosis also may be difficult. Some sections may readily show numerous colonies of the organisms. Other areas with the same typical picture may show no colonies. This difficulty frequently is commented on in the literature, and it was encountered in the five specimens examined in this study. In two specimens they were found only after careful search of many sections (Fig. 2, *b*). In the remaining specimen they were not found. It is apparent, in view of these observations, that when actinomycosis is suspected, numerous sections must be made and carefully studied before diagnosis of the disease can be made.

The treatment of pelvic actinomycosis is both surgical and medical. Most authors agree that all diseased tissue should be radically removed whenever possible. Ninety-five per cent of the patients reported on in the literature underwent surgical treatment. In the eight cases reported herein, all the patients had undergone operations before they came to the Mayo Clinic, and five underwent additional surgical procedures at the clinic.

Many forms of medical treatment have been used in actinomycosis, and the favor accorded each has undergone changes through the years. Although the different forms of therapy have been used in combinations, they will be discussed separately.

Iodides.—According to Wright, Nocard in 1892 was the first to utilize potassium iodide in the treatment of actinomycosis in man. Since that time it has been used constantly. The theory of the action of iodides is that when they are absorbed, they combine with proteins, liberating free iodide, which has the action of a counterirritant and may tip the balance in favor of the tissues by vascularizing the part and increasing leucocytic action. This may cause early softening of the tissue and extrusion of the organism. Iodine may neutralize the action of agents which prevent solution and absorption of necrotic tissue, thus laying bare the organism to real germicidal agents. In vitro, the growth of Actinomyces is not retarded by concentrations of potassium iodide up to 2 per cent. Thus, there is no scientific proof that potassium iodide is of value. However, it has been and still is used in gradually increasing doses up to 100 grains (6.5 Gm.) administered three times a day. A 10 per cent solution of sodium iodide has been used intravenously, 30 to 40 c.c. being administered the first day and the dose being gradually increased until 100 c.c. per day are being given. Iodides were used in three of the eight cases reported in this study.

Yatren.—This drug has been used occasionally. It is believed to mobilize the defense mechanism of the body rather than to exert any specific action on Actinomyces. It is given intravenously. It is a dangerous drug, since it may induce functional disturbances of the liver. It was not used in our eight cases.

Gold Vaccine.—Déak in 1941 reported that in twenty-two months, he had cured a patient of genital actinomycosis by means of gold vaccine. The patient also received roentgen therapy, but this was stated to be of no help. Gold vaccine has rarely been used.

Actinomyces Vaccine.—It was said[37] that Colebrook about 1920 attempted to carry out active immunization of the patient by the use of vaccine therapy. He came to the conclusion that it was of no value without surgical treatment also, but he noted improvement in patients for whom drainage of abscesses was carried out. Macnab used stock polyvalent vaccine in doses of 1 to 4 c.c. (1 c.c. containing 2,500,000 fragments of the mycelium) by injection on alternate days for a period of three weeks. Vaccines were not used in our eight cases.

Roentgen Therapy.—According to Gardiner and Welsh, Harsha in 1904 first used roentgen therapy on actinomycosis with success. Since 1904 roentgen rays have been used in varying doses and courses. Radium has also been used. Although roentgen rays in the form of ten erythema doses do not kill Actinomyces in pure culture, they do favorably affect the disease, probably because of the reaction of the tissue. Desjardins concluded that roentgen rays are powerful therapeutic agents against Actinomyces. McWhirter reported excellent results obtained with roentgen therapy in all types of the disease. This form of treatment was used in three of the eight cases in this study.

Thymol.—After studying twenty-two different volatile oils, Myers and Thienes[32] in 1925 and Myers[30, 31] in 1927 and 1937 advocated the use of thymol in actinomycosis. Joyce recommended a dose of 1.5 Gm. of thymol administered in capsules two days out of every three until 60 Gm. have been given, and this was to be accompanied by daily irrigation of sinus tracts with a 10 per cent solution of thymol in olive oil. Bancroft and Stanley-Brown used slightly larger doses. Thymol was not used in the eight cases reported in this study.

Sulfonamide Therapy.—Sulfonamide drugs were used for actinomycosis shortly after they had been discovered. Walker[44] in 1938 was the first to report favorable results from the use of sulfanilamide in abdominal actinomycosis. Other reports soon followed.[14] Benbow, Smith, and Grimson used various sulfonamide drugs, but preferred sulfadiazine. Lyons, Owen, and Ayers secured striking results with sulfonamide drugs in all clinical types of actinomycosis. Cutting and co-workers[7, 11, 12] found sulfathiazole and sulfadiazine to be most effective in vitro, and recommended that the concentration of the drugs in the blood be kept higher than 9 mg. per 100 c.c. In the literature there are only five reports of cases in which sulfonamide drugs were used in actinomycosis of the tubes and ovaries. Of the patients concerned, four died and the condition of one was improved. However, in the literature from 1941 to 1946 only nine cases were reported in which sulfonamide drugs were used for this disease, so that conclusions cannot be drawn on the basis of so small a series. In the eight cases reported in this study, sulfonamide drugs were used in three, with one patient being reported as cured and two as being improved.

Penicillin.—The latest drug available for the treatment of actinomycosis is penicillin. In the test tube *Actinomyces bovis* reacts poorly to penicillin when compared to the Oxford standard staphylococcus in the ratio of 1:3. However, Jones and Brownell, Walker and Hamilton, Herrell, Nichols, and Heilman and others reported favorable results from the use of penicillin in clinical actinomycosis. The sensitivity of different strains of Actinomyces varies widely, and it is therefore best, in calculation of the proper dose, to test the strain recovered in a given case in glucose broth with varying concentrations of penicillin. Most authors used huge doses of penicillin in practice. In none of the one hundred nine cases of actinomycosis of the ovaries reported in the literature did the patients receive penicillin, but penicillin has been used in actinomycosis of other organs with good results. Four of our eight patients received penicillin; two were reported as cured, one as improved, and one dying of advanced actinomycosis complicated by glomerulonephritis.

In summary of treatment, it might be well to outline Dorling's plan of therapy for abdominal actinomycosis:

Prophylaxis. Early appendectomy when appendicitis is diagnosed.
Surgery. The ideal is radical excision of diseased tissue.
Local oxygenation with hydrogen peroxide, Carrel-Dakin fluid, or zinc peroxide in suspension.
Iodides. Preferably potassium iodide in doses of 5 grains (0.3 Gm.) administered three times daily, the dose being gradually increased to 200 grains (13 Gm.) daily.
Sulfonamide drugs. Three repeated courses, with an interval of a week between courses.
Penicillin. Local instillation and parenteral injection.
Roentgen therapy.
General measures, such as rest and use of tonics and vitamins.

Of the 109 cases in the literature, 102 are accompanied by reports of results. In these 102 cases twenty-five patients, or 24.5 per cent, presumably were cured; fifteen, or 14.7 per cent, were improved, and sixty-two, or 60.8 per cent died. In the eight cases reported in this study, three patients, or 37.5 per cent, presumably were cured; three, or 37.5 per cent, were improved, and two, or 25 per cent, died. Although the present series was too small to permit the formation of conclusions as to efficacy of treatment, the results of treatment compared favorably with those reported in the literature.

Conclusions

Actinomycosis of the ovaries and Fallopian tubes is one of the less common, yet serious, diseases of the female pelvic viscera. It is a disease with which every gynecologist and abdominal surgeon should be familiar. The causative organism usually is *Actinomyces bovis*. The organism is a normal inhabitant of the alimentary tract, which usually is the origin of the infection, although entry by way of the vagina is possible. The habit of chewing grain or grasses and contact with animals or human beings afflicted with actinomycosis are not etiologic factors in the disease. The Fallopian tubes and ovaries are the usual sites of the infection. The gross pathologic picture is one of a spongy, honeycombed, granulomatous mass with adhesions and sometimes with sinuses to surrounding structures. The microscopic picture is that of multiple abscesses encased in a granulomatous fibroblastic stroma. The fungi are typically found in the abscesses and in the lining of the accompanying sinus tracts. Actinomycosis spreads by direct extension or by the blood stream. It rarely spreads by way of lymphatic vessels. The clinical picture of the disease

is not characteristic, and is similar to pelvic inflammatory disease of other causation. The positive diagnosis depends on the finding of colonies of the organism bacteriologically or pathologically. The treatment of actinomycosis of the female pelvic viscera is both surgical and medical. Radical removal of all diseased tissue is the surgical ideal. Although iodides and roentgen therapy still have a place in the medical program for actinomycosis, therapy with both sulfonamide drugs and penicillin administered in large doses over protracted periods gives the best results. In spite of radical surgical treatment and chemotherapy, the prognosis of this disease is still to be regarded as serious.

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TRANSVERSE OR OBLIQUE PRESENTATION OF THE FETUS IN THE LAST TEN WEEKS OF PREGNANCY: ITS CAUSES, GENERAL NATURE, AND TREATMENT

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THE literature shows little evidence of much attention given to transverse or oblique presentation of the fetus during the last trimester of pregnancy. We believe that such fetal position, especially if it tends to persist, is of definite clinical importance and should be considered as sufficient reason for carrying out soft-tissue x-ray studies of the uterus, in order to visualize the placenta and determine its location, the necessity for which determination will be demonstrated. The purpose of this paper is to show the principal causes and the significance of transverse or oblique presentation of the fetus in the last ten weeks of pregnancy.

The frequency of occurrence of transverse presentation at or near full term in large series of cases has varied between 0.56 per cent (Schroeder[6]) and 0.96 per cent (Williams[7]). Greenhill[8] states that it "occurs about once in every 200 cases, more often in multiparas than in primiparas and more frequently in premature labor than at term."

Studies and Results

In a recent study[9] of the soft-tissue x-rays of the uterus and cystograms taken on a series of 488 women in the third trimester of pregnancy at the Boston Lying-in Hospital, we found 39 cases of placenta previa. Four hundred thirty-two of these women were x-rayed because of third trimester uterine bleeding. The other fifty-six had routine roentgenologic studies because of transverse presentation of the fetus, and in this group 21.4 per cent had placenta previa. These cases of transverse presentation occurred during a period in which there were 14,166 deliveries at or near term at our hospital.

This paper is concerned with the presentation of a series of 52 cases of transverse presentation of the fetus discovered in the last ten weeks of pregnancy. Our series is made up of fifty cases† from our above-mentioned study and two others in which the position of the placenta was not determined by x-ray but was accurately outlined at cesarean section.

The chief purpose of our x-ray study[9] was the early detection of placenta previa, and we were able to make the x-ray diagnosis of complete previa, *before* the onset of uterine bleeding, in about 20 per cent of the instances in which this placental position occurred. As a by-product of this study we became curious about the relationship between placental position and fetal presentation. In the occasional case with breech or transverse presentation (and with an average amount of amniotic fluid) in which we have been unsuccessful in our attempts to perform external version we have felt that possibly an unfavorable position

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†The other six cases from our previous study were not used because their roentgenograms were technically inadequate for accurate visualization of the placenta.

of the placenta might be the reason for our failure. Reasoning along these lines, we were on the alert for any cases which might throw some light on our conjecture.

The following case is of much interest: I. G., Unit No. 33726, a 43-year-old gravida xi, para viii, was found by palpation to have transverse presentation of the fetus at the beginning of her thirty-fifth week of pregnancy. She had a very thin and relaxed abdominal wall, the uterus was much relaxed, and accurate palpation of the fetal parts was easily accomplished. The fetus was very mobile and an external version was readily performed, the head fitting well down into the pelvic inlet. The patient was next seen two weeks later, was again found with the fetus lying transversely, and external version was repeated. The following week oblique fetal presentation was found, and again was easily corrected by external version. One week after this last maneuver, when she was five days from term, she was admitted to the hospital in early labor, and an x-ray showed transverse presentation with the left arm and scapula presenting. The fetal thoracolumbar spine was seen to be bent into the shape of a horseshoe, and section was done at once, an active 7 pound, 3 ounce infant being delivered. The placenta was quickly palpated prior to its separation and was found to be implanted wholly in the fundus.

This case exemplified the fact that when the fundus of the uterus is entirely filled by the placenta there is no room in it for a pole of the fetus, the usual fundal space being already filled and obliterated. This patient also had such a marked degree of fetal hypermotility, due to the presence of an average amount of amniotic fluid, a very thin and relaxed abdominal wall, and the uterine relaxation of a para viii, that the tendency for the fetus *not* to remain in the position of cephalic presentation was as great as was the ease with which we could perform an external version and place it in that position. Even though we could turn the head well down over the pelvic inlet in left occipitotransverse position, we could not make the breech remain centrally in the fundal pole of the uterus; it would always settle back into the right lateral uterine wall region as soon as we ceased holding it.

Etiology

Taking our cue from the case reported above, we studied the soft-tissue x-rays of the uterus and the cystograms on our series of transverse presentation cases and determined the location of the placenta in each instance. We found 92.3 per cent of the placentas lay in one pole or the other of the uterus. We then obtained, for purposes of comparison, the statistics on the normal frequency of the various placental positions in the uterus. The most reliable figures seemed to be those determined by Gusserow[10] at cesarean section and by Holzapfel[11] through the utilization of the fetal membranous sac distention and flotation method (which is briefly described in the second footnote under Table II). The gross results of this comparison are shown in Table I.

Table I shows roughly that the less common placental implantations in the upper and lower poles of the uterus are in great preponderance in transverse fetal presentation, and that the most common positions, implantations on the anterior and posterior walls of the uterine body proper, are present at a rate of only 9 per cent of normal occurrence. Such wide deviations from the normal, with regard to the position of the placenta in the uterus, would certainly seem to make placental implantation in either pole of the uterus a prime causal factor in transverse presentation of the fetus.

Careful study of all of our x-ray films has allowed us to break down the more common placental positions into twelve general groups. These are diagrammatically sketched in Fig. 1, the sketches having been adapted from anteroposterior and lateral x-ray views of the pregnant uterus in the last trimester. The general group with fundal implantations of the placenta are pictured in sketches

1, 2, 3, and 4. Sketches 5 and 6 show the two most common implantation sites, since about three-fourths of all placentas are attached to either the anterior or posterior wall of the uterine body proper. The "lower uterine segment" group of placental positions are pictured in sketches 8, 9, 10, 11, and 12. A low lateral wall placental implantation does occur, but only rarely, and we have omitted it in an attempt to simplify our grouping as much as possible. In a lateral wall implantation, as pictured in sketch 7, there is practically always one border of the placenta crossing the midline of either the anterior or posterior uterine wall, but never both of them unless it is bilobed. This sketch pictures a small portion of the placental border on both the anterior and posterior walls merely to show that both do occur. In sketches 11 and 12 we have pictured both lateral and posterior wall partial and marginal previas in order to demonstrate both types, but we did not show anterior wall previas, although they are as common as those on the posterior wall, in order not to complicate the sketches. No x-ray visualization of the placenta is possible in anteroposterior films of the implantation sites pictured in sketches 5, 6, 8, and 9, so none is shown.

TABLE I. GENERAL POSITIONS OF THE PLACENTA IN SITU IN THE UTERUS IN CASES WITH TRANSVERSE PRESENTATION OF THE FETUS, COMPARED WITH CASES IN WHICH THE VARIOUS FETAL PRESENTATIONS WERE OF AVERAGE OCCURRENCE

	POSITIONS OF PLACENTA IN THE UTERUS		
	IN THE GENERAL FUNDAL REGION	GENERALLY LIMITED TO THE UTERINE BODY PROPER	ENTIRELY OR PARTLY IN THE LOWER UTERINE SEGMENT† (INCLUDING PLACENTA PREVIA)
Author's series of 52 cases with transverse lie of the fetus	48.2 per cent	7.6 per cent	44.2 per cent
A series of 207 cases with normal occurrence rates for the various fetal presentations*	14.8 per cent	84.2 per cent	1.0 per cent

*This group is a combination of the figures of Holzapfel and of Gusserow. For a description of them see the second and third footnotes to Table II.

†We refer here to the lower uterine segment as being, roughly, the lower one-fourth of the gravid uterus in the last third of pregnancy, even though it has not yet been thinned out and elongated by labor into its characteristic state.

In a previous paper,[9] in which we accurately located the placenta in 98 per cent of a series of 474 cases, we outlined our "soft-tissue" x-ray technique and explained the common difficulties met with in x-ray localization of the placenta; for these details we refer the reader to that paper. In Table II we present the rate of occurrence of the 12 various placental positions in that series, along with those of Holzapfel[11] and Gusserow,[10] for purposes of comparison with our findings in the fifty-two cases of transverse presentation reported in this paper.

Table II shows the occurrence of fundal placenta and placenta previa to be almost the same in transverse presentation of the fetus. It also points out that the presence of the placenta in the mid-portion of the posterior uterine wall or on one of the lateral walls of the mid-portion of the uterine body proper does not *permit* the fetus to lie transversely to the normal longitudinal polarity of the uterus; with the placenta in one of these two positions the polarity of the amniotic sac is strictly the same as that of the uterus itself, and the sac may have the general shape of a slightly flattened or elongated egg (see Fig. 1, Nos. 6 and 7). In a sac of such shape the fetal polarity must nearly always be longitudinal like that of the uterus, and the fetus is *obliged* to present

either by head or by breech. When the placenta is implanted on the mid-portion of the anterior uterine wall, as is shown in Table II, it is possible in only a few instances for the fetus to lie transversely. This is probably due to the fact that the anterior uterine wall, being supported by the slightly flexible and elastic abdominal wall, has some opportunity of passive expansibility. Such liberty of slight expansion is denied the posterior uterine wall since it is firmly splinted at all times by the adjacent spinal column.

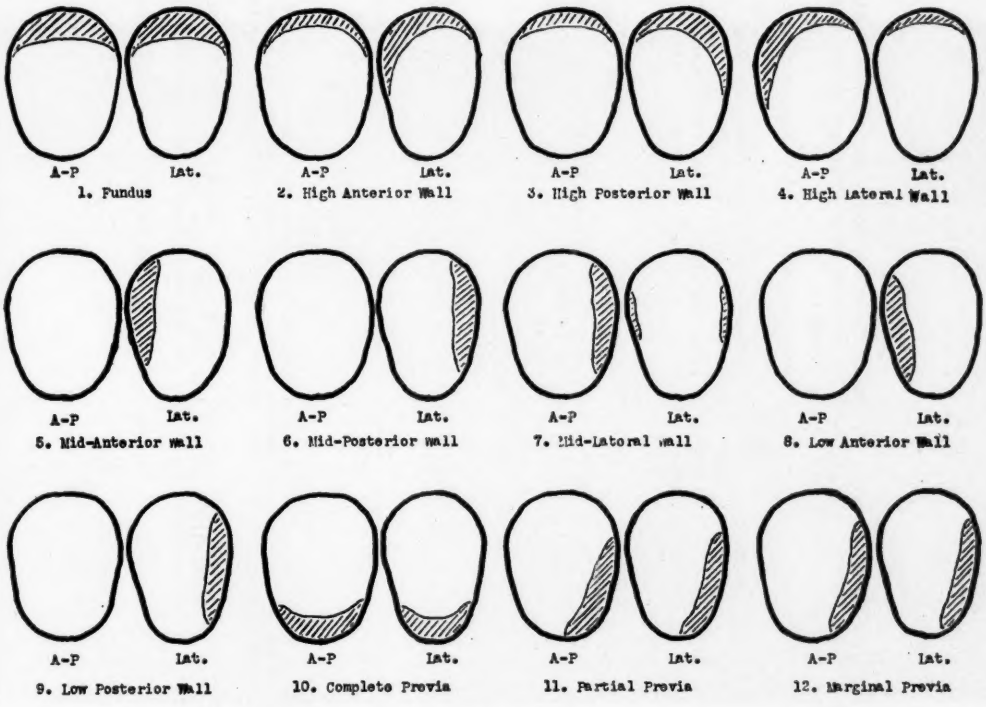


Fig. 1.—The above diagrammatic sketches show the twelve typical general positions in which the placenta is implanted in the uterus. Adapted from actual soft-tissue placentography x-rays, they picture the placental implantation sites listed in Table II. In each group, the diagram on the left shows the view, if any, of the placenta as seen in the anteroposterior film of the uterus, while that on the right represents the view of the placenta as seen in the left lateral film of the uterus. The relative proportions, as to size and shape, of the uterus and placenta in each case are roughly accurate.

These sketches graphically demonstrate the effect that the position of the placenta has upon the shape of the amniotic sac, i.e., the available fetal space.

When the placenta lies in the fundus or the lower uterine segment the amniotic sac ovoid has its longitudinal or vertical length very appreciably decreased,* so that it becomes more nearly spherical and its length may be equal to or only slightly greater than its greatest transverse width. In these circumstances its shape is roughly that of an egg with one of its ends crushed inward. In the case of a fundal placenta, to pursue the analogy, it would be the larger end of the egg that is flattened, and in the case of a central placenta previa the smaller or more pointed end of the egg would be indented (Fig. 1). In either of these circumstances there is only one empty pole of the amniotic sac in which

*The average thickness of the in situ placenta in its central portion is about 6 cm., as computed from x-ray placentography films. The average length (longitudinal) of the term uterus is about 32 cm.[12] In the case of a central placenta previa or a placenta implanted centrally in the fundus the length of the available space in the uterine cavity would be reduced to about 26 cm. which constitutes nearly a 20 per cent decrease in this dimension.

TABLE II. SPECIFIC POSITIONS OF THE PLACENTA IN THE UTERUS, EXPRESSED IN PERCENTAGE OF OCCURRENCE, IN A SERIES OF 52 CASES WITH TRANSVERSE PRESENTATION OF THE FETUS COMPARED WITH 3 OTHER SERIES, IN 2 OF WHICH THE INCIDENCES OF THE VARIOUS FETAL PRESENTATIONS MOST PROBABLY WERE NORMAL

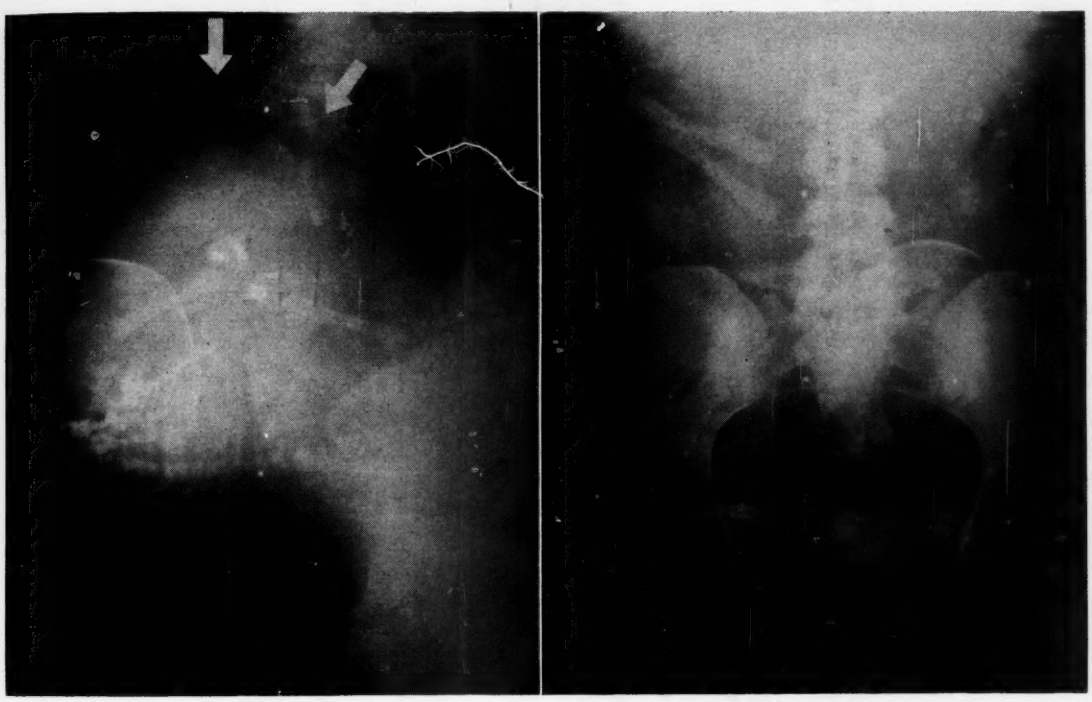
VARIOUS SERIES OF CASES	POSITIONS OF PLACENTA (SEE FIG. 1)												
	FUNDUS	HIGH ANTERIOR WALL	HIGH POSTERIOR WALL	HIGH LATERAL WALL	MID-ANTERIOR WALL	MID-POSTERIOR WALL	MID-LATERAL WALL	LOW ANTERIOR WALL	LOW POSTERIOR WALL	COMPLETE PLACENTA PREVIA	PARTIAL PLACENTA PREVIA	MARGINAL PLACENTA PREVIA	TOTALS
Transverse or oblique lie of the fetus (52 cases)	25.0	15.4	5.8	2.0	7.6	0	0	11.6	5.8	11.6	7.6	7.6	100
	Generally fundal group total: 48.2							Lower segment group: 44.2		26.8 total			
All presentations (author's series of 474 cases)*	7.4	1.9	0.9	2.0	33.1	28.9	7.7	8.8	1.8	7.5 total			100
Holzapfel's series (107 cases)†	6.6	not mentioned	not mentioned	13.0	35.5	33.6	10.4	not mentioned	not mentioned	0.9 total			100
Gusserow's series (100 cases)‡	9.0	not mentioned	not mentioned	1.0	40.0	37.0	12.0	1.0	not mentioned	none			100

*A series of soft-tissue placentography x-rays taken of 474 consecutive cases of vaginal bleeding or transverse lie of the fetus in the third trimester of pregnancy.[9] The fetal presentations in this series, because of its nature, were: 77 per cent cephalic, 11.1 per cent breech, and 11.8 per cent transverse. Since in 52 of the cases the fetus presented transversely, the slight increase in incidence of fundal placentas is to be expected.

†A series of placentas with attached membranes from 107 practically consecutive deliveries in which the incidences of the various fetal presentations probably were normal. Holzapfel described these at length.[11] He closed the fetal exit tear in the membranes, then filled the amniotic sac with water and floated it in a tank of water. The two bilateral bulges of the sac, denoting the positions of the uterine cornua, localized the position of the placenta within the uterus.

‡A series of 100 unselected parturient women, described by Gusserow,[10] in which the placental location was determined at section.

a pole of the fetus can lie. The other fetal pole, being displaced by the placenta which fills the other uterine pole, must lie against one of the walls of the mid-portion of the uterine body (Fig. 2, Film B). Since the posterior uterine wall contains a shallow indented longitudinal groove resulting from its continual approximation to the lumbar spine, and since the anterior abdominal wall, if not appreciably relaxed, keeps the anterior uterine wall slightly flattened, the natural accommodation for the free or displaced fetal pole is afforded by one of the lateral walls of the uterine body proper. With one fetal pole thus displaced



A. *B.*

Fig. 2.—The above x-rays are lateral and anteroposterior films taken of the same patient at the beginning of her thirty-seventh week of pregnancy. They show fundal implantation of the placenta and transverse presentation of the fetus.

R. V. (Unit No. 37913, x-ray No. 25010), a 29-year-old gravida iv, para iii, had the above x-ray studies because transverse presentation was discovered at routine palpation when she was three weeks from term. When seen one week later her fetus was presenting by breech, so an external version was done. Ten days following this she was admitted to the hospital in early labor. The presentation was cephalic, and she delivered spontaneously in three and one-half hours. Her placenta, as might be expected, was expulsed from the uterus by the mechanism of Schulze; the third stage was fourteen minutes in duration.

Film *A* shows the fundus of the uterus (outlined by arrows) to contain the placenta. The fetus and its enveloping amniotic sac occupy the lower two-thirds of the uterine cavity. In this film the fetus lies transversely, while in Film *B* it is presenting obliquely. In Film *B* the bladder is seen to contain radiopaque solution, and the bladder shadow delineates the lowest extension of the lower uterine segment.

laterally, or transversely, from the usual longitudinal fetal polarity there is little effective splinting force (particularly in grand multiparas) to hold the other fetal pole centrally either in the lower uterine segment or in the fundus (whichever of these does not contain the placenta). Under these conditions the fetal pole which lies in the empty pole of the uterus tends to float out and away from its natural berth and to lie against the immediately adjacent portion of the lateral uterine wall on the side opposite from that in which its other already displaced pole is resting (Figs. 2 and 3). And thus we have the fetus in transverse or oblique presentation.

TABLE III. PERCENTAGE OF OCCURRENCE OF SOME DEFINITE AND PROBABLE CAUSES OF TRANSVERSE PRESENTATION OF THE FETUS IN THE LAST 10 WEEKS OF PREGNANCY: A COMPARISON* BETWEEN THE ETIOLOGIC FACTORS FOUND IN THE AUTHOR'S SERIES AND THOSE LISTED BY COLE AND DELANEY[5]

		PROBABLE OR DEFINITE CAUSES OF TRANSVERSE FETAL LIE OR PRESENTATION											
		UNUSUAL PLACENTAL POSITION			CEPHALO-PELVIC DISPRO-PORTION: CON-TRACTED PELVIS	HYDRAM-NIOS	EFFECT OF TUMORS		FETAL DEATH IN UTERO	UTERINE FACTORS		ABDOMINAL WALL FACTORS	
COM-PARATIVE SERIES	DEGREE OF MULTI-PARITY (AVER-AGE)	PLACENTA PREVIA	PLACENTA IN FUNDUS	PLACENTA HIGH OR LOW IN THE UTERUS			MYOMAS OF THE UTERUS	EXTRA-UTERINE PELVIC TUMORS		PREVIOUS SUSPEN-SION OF UTERUS	ABNOR-MAL UTERINE SHAPE	VENTRAL HERNIA	RELAXED ABDOM-INAL WALL
Author's series (52 cases)‡	3.6	27	25	40.6†	7.7	2	0	0	2	0	0	0	23
Series of Cole and Delaney (78 cases)	2.8§	10	not men-tioned	not men-tioned	6.4	2.6	11.5	1.3	not men-tioned	3.8	9.0	3.8	not mentioned, other than hernia

*Since all of the 78 cases described by Cole and Delaney were those of women who had transverse presentation at the time of the onset of labor or when section was done, and since this was true in only 36.5 per cent of the author's series of 52 cases, this comparison is not actually a very valid one. It is used, however, because theirs seems to be the most representative of recent writings on this subject.

†Derived from Table II.

‡The percentages in this series are not figured on the basis of 100 per cent total, because more than one factor was frequently operative in the same case.

§This figure is adapted from the figure of 1.8 listed in the article by Cole and Delaney because they have followed the practice of terming as a para i a woman we have termed a para ii. In this paper we refer to a woman in the third trimester of her first pregnancy as being a para i. A woman in the last third of her second pregnancy, not counting her miscarriages, is referred to as para ii, etc.

That transverse presentation does not occur in the latter weeks of pregnancy in all cases of fundal placenta is shown by Table II. From this table it can readily be calculated that in the author's series of 474 cases studied by x-ray[9] there were thirty-five with fundal placentas, whereas in only thirteen, or 37 per cent, of these was transverse presentation of the fetus known to have occurred.

In further pursuance of the question of the etiology of transverse or oblique presentation we have compared our series of cases with those of Cole and Delaney[5] in Table III.

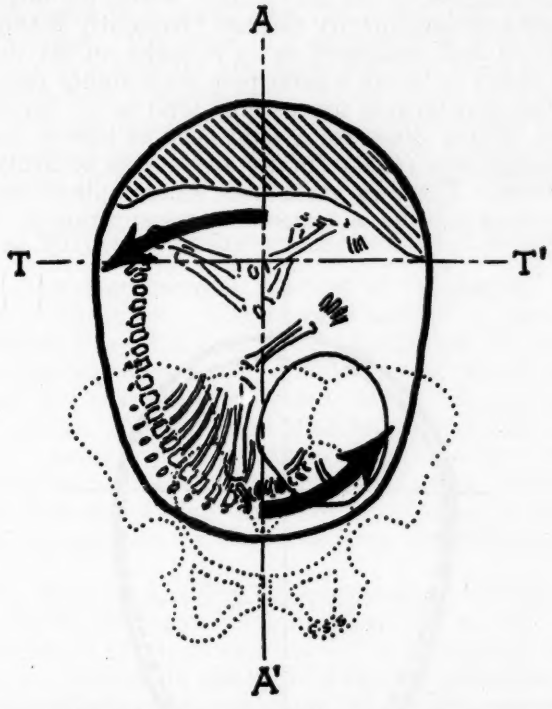


Fig. 3.—This diagrammatic sketch was adapted directly from the x-ray pictured in Fig. 2, Film *B*. Lines AA′ and TT′ denote the greatest length and width of the uterus, respectively, and TT′ shows the level at which the Fallopian tubes come off the cornua.

The placenta, as indicated by the cross-hatched area, is implanted in the fundus, and the fetus lies in oblique presentation with its head in the left iliac fossa and its breech in the right cornual region. The placenta, while implanted solely in the fundus, has a slight majority of its bulk to the left of the mid-line. The upper arrow shows the direction in which the breech is displaced laterally from the fundal region. The lower uterine segment is seen to have a shallow curvature, and the lower arrow shows the direction in which the head is displaced laterally from the midline of the pelvic canal against the adjacent lower portion of the lateral uterine wall.

We believe, to the best of our knowledge, that our series is the first in the world literature to point out the causal role of completely fundal placentas in transverse or oblique presentation of the fetus (See Table III). Furthermore, as was shown in Table I, we believe that the presence of the placenta implanted wholly or mostly in either the fundus or the lower uterine segment of the uterus was the most potent cause for this position of the fetus in 92.3 per cent of our series of cases.

Multiparity, which we believe is the next most important cause in our series, is one which is necessary when the placenta is implanted in the fundus. The average parity of our series is 3.62 (in the generally fundal group there were only two primiparas), while that of all the patients delivered in our hospital

during the period from which our series was drawn was 2.38. Thus the factor of greater than average multiparity, acting in conjunction with the presence of the placenta in the fundus or the lower uterine segment of the uterus, produces the common situation in which transverse presentation of the fetus occurs.

We believe that multiparity acts primarily through the medium of relatively greater relaxation of the uterine walls, and secondarily through relaxation of the abdominal wall, when this is also present. This view is given some support by the commonly observed fact that the greater the degree of multiparity the less frequently the head engages in the pelvic inlet before the onset of labor. Thus, the greater the degree of multiparity the less frequently is the lower pole of the uterine cavity pointed and elongated so as to make an inviting deep concavity in the bony pelvic canal in which a fetal pole may snugly rest. In other words, the lower pole of the multigravid uterus may tend to be, for practical purposes, a relatively shallow resting place for a fetal head or breech, and one which does not offer a deep enough concavity to invite any degree of fixation or engagement of a pole of the fetus. Thus, in cases with fundal placentas, the multigravid uterus tends to promote oblique or transverse presentation of the fetus (Fig. 4).

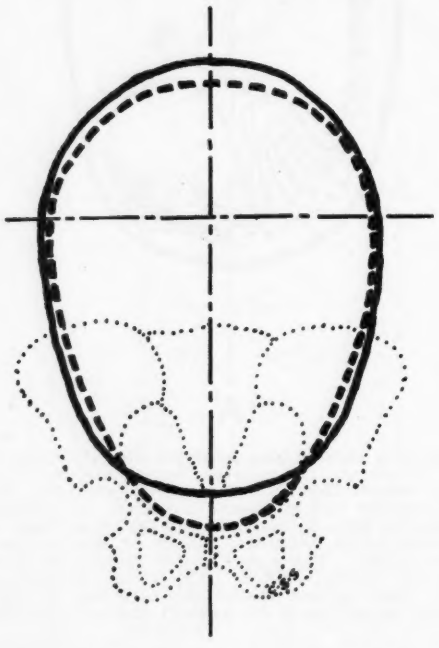


Fig. 4.—The above composite diagrammatic sketch was adapted from the anteroposterior soft-tissue placentography x-rays of several cases.

The outer solid line delineates the general shape of the multigravid uterus at or near term, and was adapted from several x-rays of multiparas in which engagement of the presenting fetal pole had not yet taken place. The inner broken line depicts the average shape of the primigravid uterus, at or near term, in which the presenting fetal pole is engaged.

The more deeply pointed lower pole of the uterus and the lower general level of the lower uterine segment of the primigravid organ at term are characteristic of it when lightening has taken place.

The shallow curvature of the lower uterine segment and its relatively high level with regard to the pelvic inlet are characteristic of the multigravid uterus at or near term.

This situation in the relaxed, multigravid uterus allows the unengaged fetal pole to "float" laterally away from the central axis of the pelvic inlet, or, in cases in which there is also marked relaxation of the anterior abdominal wall, to override the symphysis pubis anteriorly.

The combined potentialities of the factors of a fundal or lower segment placenta and multiparity in causing transverse presentation of the fetus are further enhanced, we believe, by the presence of such additional factors as contracted pelvis, hydramnios, fetal death in utero, relaxed abdominal wall and ventral hernias. Since we happened to have no cases of myomas of the uterus in our series (none of our patients were Negro women), nor any patients with extrauterine pelvic tumors, these conditions played no causal role in the cases we are presenting here. We have seen, of course, occasional women in whom a cervical or lower uterine segment myoma has filled a large portion of the bony pelvic canal, and in such cases this tumor was the undoubted chief cause of oblique presentation of the fetus. We agree that an abnormal shape of the uterus, such as would be the case in a slightly bicornate one, can itself alone be the cause of oblique or transverse fetal presentation. Fetal death in utero occurred in one of our cases, but this patient also had a low anterior wall placenta and was a 40-year-old para iii, so it is difficult to estimate just how potent a causative role the fetal death played in the production of transverse presentation in her case.

General Nature of Transverse Presentation of the Fetus

There are certain characteristic features of the general situation in transverse presentation of the fetus. The average parity* of the twenty-five women in whom the placenta was wholly or mostly implanted in the fundus was 4.38, and their average age was 33.6 years. The parity of the twenty-three women in whom the placenta was a previa or very low implanted was 2.97, and their average age was 32.7 years. Thus, in cases with completely fundal or very high implanted placentas, a necessary high degree of multiparity *must* act in conjunction with this placental position in order to bring about transverse presentation. It is likewise seen that such a high degree of multiparity is not necessary in producing transverse presentation of the fetus when the placenta is a previa or low implanted.

The transverse fetal lie was first discovered at an average duration of pregnancy of 33.7 weeks, the extremes being 31.4 and 35.7 weeks. There is no appreciable difference between the apparent time of occurrence of transverse lie of the fetus in placenta previa and in those with fundal placentas in our series as a whole (by actual calculation the transverse lie was discovered 5½ days later, on the average, in the fundal group).

Fetal motility was greatest in the four patients with anterior wall placentas, but was generally marked in the cases in which the placenta was implanted entirely or mostly in the fundus. This is exemplified by the fact that the frequency of spontaneous version to cephalic presentation was nearly three times greater in the fundal group than in the lower uterine segment group, which is readily understandable when one considers the greater parity of the fundal group and the partial or complete filling of the lower uterine segment by the placenta in the lower segment group. Spontaneous version to cephalic presentation occurred in 27 per cent of the patients, external version was done in 40.4 per cent, and in the remaining 32.6 per cent electively it was not done. When transverse presentation was first discovered x-rays were taken at once. If the fetus still presented transversely when the patient was next seen, which was usually after an interval of one to two weeks, external version was performed unless there were contraindications to this procedure. We did not attempt external version if hydramnios was present, elective section was already planned at term, the patient was too far along in labor when transverse presentation was first discovered, there was fetal death in utero, uterine bleeding was present, or placenta previa had already been diagnosed by x-ray.

*See fourth footnote under Table III.

In some recent papers on soft-tissue x-ray placentography,[13, 14] it has been stated that the fetus nearly always faces the placenta, and Dipple and Brown[14] found this to be true in 95.8 per cent of their series of 259 patients. Such was the case in three-fourths of our cases of transverse presentation of the fetus, but in one-fifth of the patients the fetal back lay next to the placenta. In the group with fundal placentas 88 per cent of the fetuses faced the placenta, while this was true in only 65 per cent of the cases in the lower segment group. With the exception of one case the remainder of the fetuses in these two groups lay with their backs to the placenta. The situation in which a fetal side lies adjacent to the placenta is of necessity practically limited to those cases in which the placenta is implanted on either the anterior or the posterior wall of the uterine body proper. This occurred in two of our four cases with anterior wall placentas.

In only 36.5 per cent of our patients were the fetuses still in transverse presentation at the time of section or the onset of labor. 11.5 per cent of the fetuses had turned spontaneously to breach presentation, and in the remaining 52 per cent spontaneous or external version to cephalic presentation had been effected.

Treatment

Thirty-four, or 65.4 per cent, of the patients were delivered by the vaginal route, while the remaining eighteen had cesarean section. Twenty-four of the women either delivered spontaneously or had a simple low-forceps delivery. Four patients were delivered by breech extraction, and one woman, with bleeding from a marginal placenta previa in her thirtieth week of pregnancy, was bagged, and subsequently delivered a 2 pound, 12 ounce infant spontaneously. Braxton Hicks' version and extraction were performed on three women because of bleeding from partial or marginal placenta previa at 29, 29, and 32 weeks of pregnancy, respectively, and it was also done on a fourth patient because of uterine bleeding from partial premature separation of a normally implanted placenta (high anterior wall) with onset of weak labor at 28 weeks of pregnancy. Decapitation was resorted to in one case with transverse presentation and fetal death in utero at 35 weeks of pregnancy after the patient had gone into weak labor and presented one arm and scapula.

Cesarean section was done in eighteen (34.6 per cent) of the fifty-two cases in this series.

The one section in the fundal group was done because of transverse fetal lie, the left shoulder and arm presenting and the spine flexed in the shape of a horseshoe, as was demonstrated on the x-ray film. This woman went into strong labor shortly following admission and the fetal heartbeat became irregular. The infant weighed 7 pounds, 3 ounces, and survived. The one section in the "High Anterior Wall" group was done because of cephalopelvic disproportion. Of the two women in the high posterior wall placenta group, one had a routine repeat section because of cephalopelvic disproportion, and the other, a case of hydramnios, developed a rigid and irritable uterus and a weak pulse after twenty-one hours of fruitless labor. At section the placenta in this case was found to be completely separated and there was a 1,200 c.c. blood clot in the uterus.

In the group of patients who had anterior uterine wall placentas, two had cesarean delivery, both of which were repeat sections. Twelve of the twenty-three women in the lower uterine segment group, or 52 per cent, had sections. Two of these had placentas implanted low on the posterior uterine wall, and their cesareans were done because of repeat section for cephalopelvic disproportion in one case and hemorrhage from partial separation of the placenta with transverse presentation and weak labor in the other. Of the fourteen patients with placenta previa, ten had sections, six of them because of complete previa. Of the remaining four cases, two were sectioned because of partial and two

because of marginal previa. The two women upon whom section was performed because of partial placenta previa had uterine bleeding and oblique presentation of viable fetuses; both infants survived. One of the patients with marginal previa had transverse presentation and uterine bleeding during labor. The bleeding increased following sterile vaginal examination, so section was done at once. The other woman with marginal previa had breech presentation and continuous uterine bleeding, and section was done immediately following the sterile vaginal examination which confirmed the presence of placenta previa.

No deliveries were accomplished by the rare mechanism of conduplicato corpore.

Twenty-eight women in our series had labor, and its average duration was 6.2 hours. The average duration of labor for the group of women in whom the placentas were implanted wholly or mostly in the fundus was 6.1 hours, and the average parity for this group was 4.1. We have not been able, in the group of women who had labor, to demonstrate any relationship between placental position and the duration of labor. The average duration of the third stage of labor was longest (15 minutes) in those cases in which there were purely fundal implantations of the placenta, and this duration is roughly twice as long as average for our hospital as a whole.

Results

The average birth weight of the baby in the generally fundal group was 7 pounds, 1 ounce, and since all the babies in this group were born at or within two weeks of term there is no evidence that fundal implantation of the placenta results in any deviation of the birth weight from the normal average.

All of the fifty-two mothers survived and, when their various pathologic conditions are considered, there was no increase in morbidity. 79 per cent of the infants survived, although three of them were premature. There were seven stillborn infants, which was 13.4 per cent of the total series. Three of these cases of stillborn infants occurred in the generally fundal group. The first of these died in utero following the onset, at 26 weeks of pregnancy, of bleeding, spontaneous rupture of membranes, and consequent labor; his birth weight was 2 pounds, 7 ounces. The second stillborn, a case in which the placenta was implanted high on the anterior uterine wall and in the fundus, had disappearance of heart sounds during labor, and at birth there was a tight loop of umbilical cord around his neck; his birth weight was 7 pounds, 4 ounces. The third infant died in utero as a result of complete abruptio placentae, and weighed 8 pounds, 1 ounce. In the group with placentas implanted low on the anterior uterine wall there were two stillborn infants. One died in utero at 35½ weeks of pregnancy, cause undetermined. In the second case there was spontaneous rupture of membranes at 31½ weeks of pregnancy, with prolapse of a leg and subsequent protrusion of the foot from the vaginal orifice. At full dilatation of the cervix, breech extraction was performed but the aftercoming head became impounded above a Bandl's ring, and had to be perforated.

There were four neonatal deaths, two of which occurred in the group in which the placenta was implanted in the fundus.

One of the babies in the fundal group delivered following spontaneous onset of labor in the 28th week of pregnancy; he weighed 2 pounds, 7 ounces, and died of prematurity. The other infant in this group had fetal distress toward the end of labor and was born with one tight loop of cord around his neck. He was very limp at birth, and respirations were not established until after thirty minutes of resuscitation. He weighed 6 pounds, 1 ounce, and lived only a few hours. The placenta had been implanted high in the fundus and thus, although the cord was of average length, the infant had just about reached "the end of his tether" by the time the vertex had descended below the spines. Although the

mother had been given oxygen by mask during the last one and one-fourth hours of labor because of the irregularities of the fetal heart, this infant apparently had suffered sufficient strangulation, with interference of the blood circulation through the major vessels of the neck, to have irreversibly compromised the main functional centers in the medulla. The other two neonatal deaths occurred in cases with marginal placenta previa. One of these infants weighed 2 pounds, 12 ounces, and was born following bagging because of uterine bleeding at 30 weeks of pregnancy. He died of prematurity after 3½ hours. The other of these infants was delivered by Braxton Hicks' version and extraction because of uterine bleeding at 32 weeks of pregnancy. He weighed 3 pounds, 2 ounces, and died of prematurity a few hours following birth.

Discussion

We have shown that when the placenta is implanted in the fundus or the lower uterine segment of the uterus it causes a considerable change in the shape of the amniotic sac cavity in which the fetus lies. The average measurements of the uterine cavity[12] at or near term are: length, 32 cm.; greatest transverse width, 24 cm.; and anteroposterior depth, 22 cm. Since the average thickness of the central portion of the placenta is about 6 centimeters,[13] the length of the amniotic sac cavity may be decreased, when the placenta is implanted in the funds or lower segment of the uterus, to about 26 centimeters, and thus the horizontal width and vertical length of the amniotic sac can be practically the same. In such a case the fetus apparently could lie transversely to the longitudinal axis of the uterus as easily as it could present by either the head or breech. The position of the placenta, we believe, is the chief determinant of the *shape* of the amniotic sac, or available fetal space, and the *size* of this space, aside from the progressive increase as pregnancy advances, depends upon the relative amount of amniotic fluid present and the relative size of the fetus.

In cases of central, or complete, placenta previa, transverse presentation is the most common position of the fetus, since we found it to occur in 56 per cent of a recent sampling series of cases of complete placenta previa.[15] Our study has shown that the factor of high multiparity does not play a very important causal role in producing transverse presentation in cases of placenta previa; the position of the placenta alone can prevent the presentation of one of the fetal poles in the pelvic inlet in these cases. When the placenta is implanted wholly in the fundus transverse presentation of the fetus occurs in only 37 per cent of the cases, and does so only when a relatively high degree of multiparity is acting in conjunction with the fundal position of the placenta.

It was seen that a tight loop of the umbilical cord encircling the neck of the fetus was the apparent cause of death in two full-term infants in our series. One was stillborn and the other breathed only after thirty minutes of resuscitation, expiring a few hours later. In both of these cases the placenta was implanted wholly or mostly in the fundus of the uterus, the cords were of average length, and the presentation was cephalic. Since in these cases the cord had to extend from the placenta in the fundus of the uterus down to and around the fetal neck (which, in the second stage of labor would be at about the level of the superior strait) and then back up to the infant's umbilicus, it would have to be longer than the average length of 55 cm.[16] in order not to be drawn taut by the descent of the fetus during the latter part of labor. Thus the combination of fundal implantation of the placenta and a loop of cord around the fetal neck, in cases of cephalic presentation, constitutes a definite fetal hazard if delivery is accomplished by the vaginal route. In two of the eighteen cases in our series in which the placenta was implanted in the general fundal region and delivery occurred through the pelvic canal, the cord encircled the neck of the infant. In both cases the loop was found to be tight at delivery and both infants were lost. Under these special conditions in our series the fetal mortality, thus, was 11 per cent. External version had been performed once on both of these women, but we know of no statistics which prove that the utilization of this maneuver causes a higher incidence of encirclement of the fetal neck by the umbilical cord. There were no instances of tight loops of cord around the fetal neck in any cases in our series other than those in which the placenta was implanted in the general fundal region.

A curious fact, but one of small clinical importance, is the prolonged third stage of labor found in the fundal implantation group. Since the separated placenta has further to travel before expulsion by the uterus in this group of patients than in the other placental groups, is it reasonable to expect that the expulsion process requires a longer time?

From a therapeutic viewpoint, we believe that soft-tissue placentography x-rays, and cystograms when indicated, should be taken on all women in whom the fetus presents transversely during the last ten weeks of pregnancy. The first reason for making these studies is to determine the existence or nonexistence of placenta previa, as this condition was present in fourteen, or 27 per cent, of the cases in our series. A second reason is to learn if the placenta, if not a previa, is implanted in the fundus. If the placenta is found to occupy the fundus and if cephalic presentation is present, one can be on the alert for possible fetal distress during the latter part of labor, and being thus forewarned can be prepared to take whatever steps are indicated by the particular nature of the given case.

From the aspect of preventive therapy, we recommend the performance of external cephalic version after the thirty-fourth week of pregnancy in all those cases in which it is not contraindicated. This was performed on 40 per cent of our patients which, with the occurrence of spontaneous version in another 27 per cent, was a great factor in making possible the delivery of 46 per cent of our women by cephalic presentation through the pelvic canal, and 7.7 per cent by breech extraction. In many cases the fetus will not remain in cephalic presentation following external version, but we recommend repeating the maneuver as many times as is necessary in order to insure against the occurrence of spontaneous rupture of the membranes and onset of labor with the fetus locked in transverse presentation, which undesirable event took place only once in our series.

Finally, we believe that the basic point our study has shown is that the position of the placenta, in situ in the near-term uterus, through the manner in which it indents the amniotic sac ovoid, has a definite influence upon the presentation of the fetus in an appreciable proportion of cases, and in a subsequent paper we will treat with the characteristic placental position in breech presentation.

Summary and Conclusions

1. Our study has shown that in 92.3 per cent of a series of fifty-two cases of transverse or oblique presentation of the fetus in the last ten weeks of pregnancy the placenta, as determined by soft-tissue x-ray placentography, was implanted either in the general fundal region or the lower segment of the uterus.

2. Such placental position has been shown to decrease the longitudinal length of the amniotic sac cavity to a degree where it is almost the same as the greatest transverse width of the cavity, and thus the accommodation for the fetus in transverse presentation is almost as adequate as it is for longitudinal fetal polarity, i.e., with either the head or breech presenting.

3. It has been demonstrated that a high degree of multiparity is essential, in cases with fundal implantation of the placenta, in promoting transverse presentation of the fetus, but that high multiparity is not essential in causing this fetal presentation in cases of central placenta previa.

4. Implantation of the placenta in the fundus or the lower uterine segment and a relatively high degree of multiparity have been shown to be the two principal causative agents of transverse presentation of the fetus, but the probable additional etiologic factors of contracted pelvis (cephalopelvic disproportion), hydramnios, fetal death in utero, and relaxation of the abdominal wall were present in 7.7,2,2, and 23 per cent of our cases, respectively.

5. In only 36.5 per cent of our fifty-two patients were the fetuses still in transverse presentation at the time of section or the onset of labor. 11.5 per

cent of the fetuses had turned spontaneously to breech presentation, and 52 per cent turned spontaneously or had external version to cephalic presentation.

6. Placenta previa was present in fourteen, or 27 per cent, of our cases.

7. We recommend that soft-tissue placentography x-rays, and cystograms when indicated, should be taken of all women in whom transverse presentation of the fetus is found in the last ten weeks of pregnancy. Our reasons for this are: a. To determine the existence or nonexistence of placenta previa. b. To learn if the placenta, if not a previa, is implanted in the general fundal region of the uterus. The knowledge of such placental position, in patients with cephalic presentation, will forewarn one to be on the alert for possible fetal distress in the latter part of labor should there be a loop of umbilical cord around the neck of the infant. c. To detect any uterine or extrauterine pelvic tumors, hydramnios, fetal death in utero, gross fetal anomalies (hydrocephalus, double monsters, etc.), or abnormalities of the uterus (uterus bicornis, uterus arcuatus, or partly septate uterus).

8. We believe that external cephalic version is an important preventive therapeutic measure in women with transverse presentation of the fetus in the last six weeks of pregnancy, and that it should be performed in all cases unless it is contraindicated or impossible. As a result of our pursuance of this policy, plus the spontaneous versions that occurred (fourteen, or 27 per cent), we were able to deliver 63 per cent of our patients through the pelvic canal.

9. The basic point our study has shown is that the position of the placenta, in situ in the near-term uterus, has a definite influencing effect upon the presentation of the fetus in an appreciable proportion of cases.

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THE VAGINAL SMEAR IN POPULATION SCREENING FOR UTERINE CARCINOMA*

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INTEREST in cytology was stimulated in 1917 by Stockard and Papanicolaou,[1] who used vaginal smears in a study of the estrous cycle in guinea pigs. During the next few years, their use was largely limited to studies of physiologic cellular changes during the human menstrual cycle and in pregnancy.[4, 5] In 1931, MacCarty presented the first of three[2, 3, 6] reports dealing with the characteristics of immature cells, especially with regard to the nucleo-nucleolar ratio.

Vaginal smears were first evaluated in the detection of uterine carcinoma by Papanicolaou,[7, 8] who described the staining procedure which bears his name and which has facilitated interpretation of the cytologic picture. The appearance in 1943 of a monograph by Papanicolaou and Traut[9] initiated the present wide interest in the cytologic detection of genital carcinoma. Subsequently, many articles and a handbook on vaginal cytology have appeared.[10-26]

Whether the use of vaginal cytology is more valuable as a screening procedure or as a diagnostic method is controversial.

Papanicolaou stated: "It [the vaginal smear] is not recommended as a means of ultimate diagnosis. It should be used as a preliminary or sorting procedure and should be confirmed as a matter of routine by biopsy and tissue diagnosis."[9] Fremont-Smith, Graham and Meigs have said: "It is not our purpose that this new test should compete with the biopsy or replace that method in the diagnosis of cancer."[27] Gates and Warren declared: "Overemphasis on the statistical accuracy seems to put the stress in the wrong place. If the method is to be used as a preliminary or sorting procedure, the degree of accuracy is unimportant within reasonable limits. The thing that matters primarily is whether the method will discover cancer and initiate treatment earlier than would otherwise be done."[18]

It was decided to evaluate the vaginal smear as a population screening method for selecting a group of women in whom subsequent clinical and histologic examinations would reveal a high incidence of malignancy.

Material

Vaginal smears were obtained from 5,314 women representing three different segments of the population. The first group included 2,594 women, mostly over 30 years of age, admitted to the University Hospitals between April 1, 1947, and April 1, 1948. The second consisted of 1,482 inmates of two State mental institutions who were predominantly postmenopausal. The third was made up of 1,238 women over 30 years of age from Washington County, Iowa, who volunteered for the examination.

*This project has been supported by grants from the Iowa Division of the American Cancer Society.

Method

For the purpose of population screening it was necessary to devise a method for obtaining vaginal discharge quickly, easily, and at low unit cost. The techniques previously described were too complicated. A damp cotton swab applicator protected by a sheath was devised. The sheath was of cardboard or rubber tubing, one-fourth inch in diameter and five inches in length with one end beveled. A standard applicator stick was used (Fig. 1).

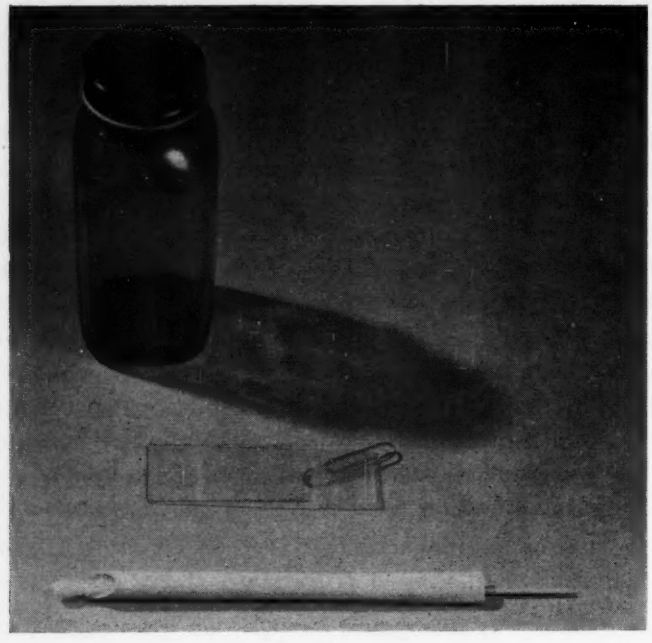

Fig. 1.—Equipment necessary to obtain a vaginal smear by the sheath method.

The sheath containing the applicator is inserted along the posterior vaginal wall to the cul-de-sac. The swab is then pushed beyond the sheath and a sample of the discharge obtained by a circular motion. The swab is then withdrawn into the sheath and the entire unit removed. The applicator is again pushed forward and the discharge rapidly smeared and tapped on a labeled, clean glass slide. Before the smear has time to dry, a matter of a few seconds, it is dropped into a small bottle containing equal parts of 95 per cent alcohol and ether. (A paper clip previously slipped over one end of the slide keeps it from adhering to other slides in the bottle.) The bottle is then stoppered securely, and the sheath and applicator discarded. By this method as many as 250 smears were taken by one individual in a single day.

In the laboratory the slides were stained by the Papanicolaou technique. They were scanned by trained technicians, and all smears presenting unusual cells were interpreted by the authors. Smears were designated as "negative," "suspicious," or "positive" for the presence of cells believed to have originated from carcinoma.

Smears were classified as negative when only normal cell types were seen, and leucocytes and erythrocytes were not prevalent. Smears were classified as positive when they contained clumps of abnormal cells, leucocytes in abundance, old or hemolyzed erythrocytes, and a "dirty" background of cellular debris and

mucus. Smears were designated as suspicious when they contained too few of the positive characteristics and yet gave the impression that they were not normal. They contained such elements as occasional aberrant cells, normal-appearing glandular cells (either in the mid-interval of a menstrual cycle or post menopausally), large numbers of histiocytes, leucocytes and hemolyzed blood. A smear was judged inadequate when too few cells were present for interpretation or when the preparation was faulty.

Every attempt was made to obtain both clinical and histologic evaluations on as many patients as possible. The University Hospitals patients were usually available for further study. Most of the women with suspicious or positive smears had thorough pelvic examinations, and biopsies were obtained in 51 per cent of the suspicious and in 95 per cent of the positive cases.

The women in the mental institutions who presented abnormal cytologic pictures were subjected to pelvic examinations and additional smears. Biopsies were obtained from 42 per cent of this selected group.

The majority of the original and repeat smears from the women of Washington County were obtained in physicians' offices. Where no physician was available, smears were taken by a trained nurse. Pelvic examinations were done and biopsies obtained either by home physicians or at the University Hospitals.

I. Proof of Method

Analysis of University Hospital Series.—

Fig. 2 presents the results obtained from the cytologic, histologic, and clinical evaluation of 2,594 women in the University Hospital series. This survey served as the basis for the evaluation of vaginal smears since the findings could be compared with those of the clinical and histologic methods commonly employed to diagnose genital malignancy.

Of the 2,594 first vaginal smears, 2,407 were interpreted as negative, 33 inadequate for interpretation, 73 suspicious, and 81 positive.

From the cytologically negative group, thirteen were later proved to have genital cancers. Eight were considered clinically positive and five clinically negative. Seven of the thirteen with false negative smears had adenocarcinomas of the uterine body as proved by curettage, and six had epidermoid carcinoma of the cervix revealed by biopsy. Second smears from eleven of these thirteen patients revealed abnormal cells. One patient had seven negative smears before abnormal cells were found, and the other had twelve negative smears. In this last case, an epidermoid carcinoma of the cervix, abnormal cells were found only after vigorously scraping the surface of the lesion.

Among thirty-three women with unsatisfactory first vaginal smears, nine were found to have genital malignancies. During the initial pelvic examination seven of the nine revealed obvious cancers; one was considered suspicious, and the other negative. Three of the group had adenocarcinomas of the body (one an adenoma malignum), and six had epidermoid carcinomas of the cervix. Adequate additional smears were obtained from four of these nine cases and three were interpreted as positive. The patient with adenoma malignum had four negative smears. No additional smears were obtained from the remaining women.

Smears from 73 patients were interpreted as suspicious. Histologic data were obtained on 39 of these women; 18 were shown to have cancer, and 21 were negative. A benign gynocologic lesion was found in each of the 21 patients after adequate clinical and histologic studies. This group included six instances of endometrial hyperplasia, five of endocervical or endometrial polyps, and ten of acute or severe chronic cervicitis. No biopsies or clinical follow-ups could be obtained on the remaining 34 patients.

Among 81 patients with positive smears, 75 were proved to have genital malignancy including three with advanced carcinomatoses on whom there was

no histologic verification. No malignancies were found in three women with positive smears even after thorough clinical and histologic examinations. The significance of the remaining three positives is unknown since the patients could not be followed clinically and no biopsies were taken.

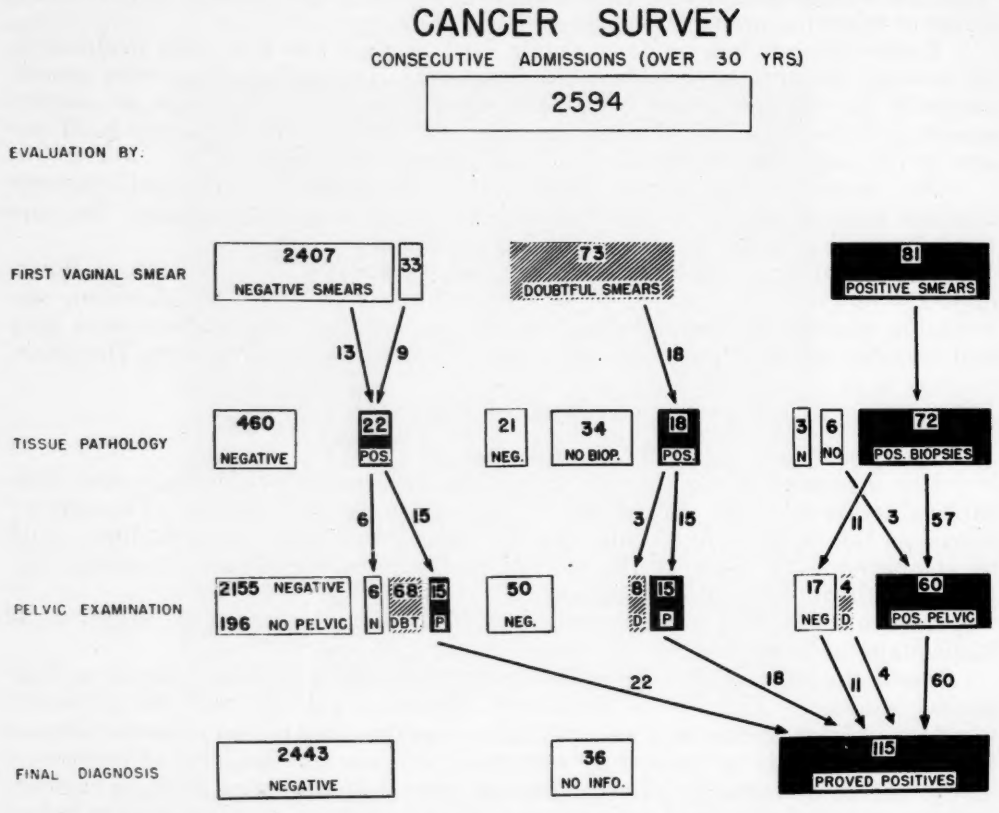

Fig. 2.—Comparison of three methods, cytologic, histologic, and clinical, in the detection of pelvic carcinoma in women admitted to the University Hospitals from April 1, 1947, to April 1, 1948.

Pelvic examinations were done on 2,398 of the 2,594 women in the hospital series. Among the 81 patients with initial positive smears, 60 had gross malignant lesions, 4 were clinically suspicious, and 17 were negative. Further clinical and histologic studies on these 17 patients revealed eleven cervical carcinomas; seven were interpreted as carcinomas in situ and four as early invasive carcinomas.

Histologic examinations were made on 636 patients (Fig. 2). Biopsies or curettings obtained from 72 of those with positive smears revealed carcinoma. No evidence of malignancy was found in 460 cases. In twelve instances the tissues submitted were inadequate for diagnosis, but subsequent biopsies from two of these patients revealed carcinoma. The initial biopsies from two patients were suspicious for malignancy; tissue obtained later showed carcinoma. In seven instances where the first biopsy was negative, subsequent tissue examination revealed a malignancy. The first biopsy from four patients showed carcinoma, but additional histologic studies before treatment could not substantiate the initial diagnosis.

In the final evaluation based on cytologic, histologic, and clinical findings, 2,443 patients were negative, 115 had proved genital cancer, and the remaining 36 were incompletely followed.

Three patients were admitted to the University Hospitals with diagnoses of genital carcinoma based on histologic studies made elsewhere. Repeated vaginal smears were negative and no histologic evidence of malignancy was found in tissue removed in this hospital. These three cases were not included in the survey.

Eight patients had ovarian malignancies; two of these women showed abnormal cells in the vaginal smear. In these two instances, laparotomy established the diagnosis of adenocarcinoma of the ovary with no evidence of uterine involvement. Apparently the abnormal cells had migrated down the Fallopian tubes to the uterine cavity and hence into the vagina.

Table I presents the histologic types of the malignancies encountered as well as the number of each in the hospital series.

TABLE I. HISTOLOGIC CLASSIFICATION OF 115 PELVIC CARCINOMAS FOUND IN 2,594 CONSECUTIVE ADULT FEMALE ADMISSIONS TO THE UNIVERSITY HOSPITALS

NUMBER OF CASES	TYPE
64	Epidermoid carcinoma of the cervix
7	Carcinoma in situ of the cervix
4	Adenocarcinoma of the cervix
30	Adenocarcinoma of the corpus uteri
3	Epidermoid carcinoma of the vulva
2	Epidermoid carcinoma of the vagina
2	Adenocarcinoma of the ovary
1	Adenocarcinoma with pelvic metastases, primary site unknown
1	Transitional cell carcinoma of the bladder involving the vaginal wall
1	Adenocarcinoma of rectum involving the vaginal wall

Summary of Results of Hospital Series.—

In the University Hospital series, the initial positive or suspicious vaginal smears corresponded with the clinical and histologic findings 93 times in 115 proved genital malignancies. In 13 patients the first smear did not detect the malignancy, and in nine the initial smear was inadequate. From 16 of these 22 patients a second smear was obtained; 14 showed abnormal cells. Genital malignancy has not yet been proved in three women presenting positive smears. However, in each instance where the smear was interpreted as suspicious or positive and adequate clinical follow-up was made, some gynecologic disorder was found.

The initial pelvic examination correlated with the final diagnosis of malignancy in 98 of 115 cases in the University Hospital series. In seventeen instances, the initial pelvic examinations failed to reveal malignancy, but, in eleven, positive cytologic findings led to further investigations which revealed the presence of carcinoma. In the remaining six patients, the malignancies were found in biopsies taken during the routine management of what had been considered benign lesions.

The initial cervical biopsy or curettings revealed carcinoma in 101 of the 115 cases of malignancy. No tissue was obtained from three patients with far-advanced carcinoma. In eleven patients the first biopsies failed to reveal the carcinoma (seven negative, two inadequate, and two suspicious); but, because of suspicious clinical or cytologic findings, subsequent biopsies were done and demonstrated malignancy.

II. The Use of the Vaginal Smear as a Screening Procedure

The University Hospital series of 2,594 women served to evaluate the vaginal smear method because findings could be correlated with clinical and histologic studies. However, if this series is reconsidered on the basis of a screening procedure the results can be listed in the same manner as those for the institutional and Washington County surveys.

From the total of 2,594 vaginal smears, 154 were suspicious or positive (Table II). The smear findings would have indicated the need for thorough clinical and histologic study of this group. When these latter studies were done, 93 cases of genital malignancies were found. In eleven instances, pelvic examinations failed to detect the presence of cancer, but tissue from seven revealed carcinoma in situ and four showed early invasive carcinoma of the cervix.

TABLE II. EVALUATION OF 2,594 VAGINAL SMEARS FROM CONSECUTIVE FEMALE ADMISSIONS TO THE UNIVERSITY HOSPITAL

2,594	Patients studied by single vaginal smears
33	Unsatisfactory smears
154	Suspicious or positive smears
2,398	Pelvic examinations
636	Biopsies
93*	Carcinomas found

*There was a total of 115 genital cancers—13 were missed by the initial adequate smear and in 9 the initial smear was inadequate for interpretation.

The survey of the inmates of two mental institutions was based on smears from 1,482 women (Table III). The slides from 43 patients were unsatisfactory and additional smears were obtained. Twenty-seven smears were suspicious or positive. Subsequent pelvic and histologic examinations on this group of 27 showed five previously undetected genital cancers, one of which was carcinoma in situ.

TABLE III. EVALUATION OF VAGINAL SMEARS FROM 1,482 INMATES OF TWO STATE MENTAL INSTITUTIONS

1,482	Patients studied by vaginal smear
43	Unsatisfactory or menstrual smears
27	Positive or suspicious smears
67*	Pelvic examinations
28	Biopsies
5	Carcinomas found

*This disproportionate number of pelvic examinations was done because of interest aroused by Ayre's speculation that high cornification counts on cervical smears are due to a concentration of estrogen in infected cervical tissues. He believes a local concentration of estrogen is a growth stimulating factor predisposing to cancer.[25, 26] Seventeen women over 62 years of age showed excessive numbers of cornified cells. Pelvic examinations were done on all of these patients and cervical biopsies obtained from three. No genital malignancy was found.

Smears were taken from 1,238 Washington County women; 1,228 were negative, six were suspicious, and four positive for abnormal cells (Table IV).

TABLE IV. EVALUATION OF VAGINAL SMEARS FROM 1,238 WOMEN RESIDING IN WASHINGTON COUNTY, IOWA

1,238	Smears obtained
10	Positive, 4; suspicious smears, 6
14	Resmears or pelvic examinations requested
6	Biopsies
3	Carcinomas found

In the four patients with positive smears, unsuspected malignancy was proved histologically in two. The third patient (E. P.) with two positive smears was subjected to

thorough clinical examination and three biopsies were obtained. One of the tissue specimens contained a small area of anaplastic squamous epithelium which was insufficient to make a definite diagnosis. This patient is to return in three months. Clinical examinations and cervical biopsies revealed no malignancy in the fourth patient who presented a positive smear. However, several subsequent smears still showed abnormal cells. She is to return for re-examination in three months.

Smears from six patients were suspicious; additional smears were obtained from five and one could not be followed. One of the repeat smears was positive, one was inadequate, two were negative, and one was retained in the suspicious category because the patient could not be followed. No tissue has been obtained to date from the woman with the positive repeat smear. The patient with the inadequate smear was clinically positive for malignancy, but no tissue could be obtained for histologic examination.

Thus, from a total of 1,238 women, the vaginal smear segregated ten patients for further study and, from these, three were found to have genital carcinoma.

In summary, the use of the vaginal smear as a screening method in these surveys selected 191 women out of 5,314. Subsequent clinical and histologic examinations led to the diagnosis of cancer in 100 of these cases, and in each of the remaining on whom adequate follow-up was made some gynecologic lesion was found.

Discussion

There are several methods of obtaining cells from the vagina and cervix. The original method introduced by Papanicolaou utilizes a curved glass tube with a suction bulb, and the discharge in the vaginal pool is aspirated and blown onto a slide. Smears made in this manner are usually thicker than those made with the applicator and sheath. The cost of the tubes and bulbs plus the breakage and time consumed in sterilizing each unit makes this technique impracticable for population screening.

Another method, introduced by Ayre,[23, 24] consists of scraping the cervix with a special wooden or metal spatula and spreading the material on a slide. This technique requires the services of a physician, the patient in the lithotomy position, and a speculum in place. This is probably the most accurate technique because visual examination of the cervix can be made and a biopsy can be obtained readily from any suspicious area. For the type of survey presented in this report, it was impossible to obtain adequate personnel, space, and equipment necessary to use this technique.

The sheath method proved satisfactory for population screening and detected a majority of the malignant lesions. The procedure is so simple that an intelligent individual can learn it in a few minutes. The rapidity is illustrated by the fact that one nurse obtained smears from the 1,482 patients in the mental hospitals at the rate of 200 daily. It is recognized that the recent use of either a cleansing douche or a lubricating jelly causes the same difficulties of interpretation here as in the other methods.

The results have been reported in total numbers rather than percentages, since the latter can be computed in many ways to stress different values. Knowing the number of cases in each category, interpretations can be made as desired. It must be stressed that a fair evaluation can be made only by comparing the initial smear with the first biopsy and first pelvic examination.

Multiple vaginal smears on the same patient increase the accuracy of this technique in the detection of genital malignancies. This survey was not designed to determine the efficiency of the vaginal smear but rather to evaluate its use in screening the general female population. Its value in this connection is indicated by the high incidence of genital cancer found in the women with suspicious

or positive smears. The liberal use of the suspicious category was believed justified by the fact that even when no malignancy was present, there was invariably some benign genital lesion present. Treatment of these lesions is not necessarily prophylactic against cancer, but it is certainly wise to eliminate any condition which might predispose to malignancy.

Certain medical and lay publications have given an erroneous impression of the diagnostic value of vaginal smears. Obtaining and preparing a sample of vaginal discharge are rapid and simple procedures but interpretation of the smears is difficult. This should not be attempted without many months of intensive study of smears from women of all ages and with a wide variety of genital lesions. The vaginal smear technique is a valuable adjunct in the fight against cancer, but it is useful only so long as it is properly evaluated and correctly used.

These data place the detection of genital cancer in a new perspective with the cytologic added to clinical and histologic examinations. In the 115 genital cancers in the hospital series, the initial cytologic examination missed 13, the initial histologic examination seven, and the initial clinical evaluaton 17. Each of the three methods alone shows a significant error rate, but, by combining all three, there is an improved chance of detecting any existing genital malignancy.

TABLE V. FREQUENCY OF DETECTION OF CARCINOMA AT THE INITIAL OBSERVATION BY THREE DIFFERENT METHODS

	NO.	PER CENT
Total number of proved malignancies	115	100
Number found positive on:		
First vaginal smear	102	88
First biopsy	108	94
First pelvic examination	98	85

Summary

A technique was devised to obtain a sample of the vaginal discharge easily, quickly, and at low unit cost. Vaginal smears were taken on 5,314 women representing three population segments: general hospital admissions, institutional inmates, and the female population of an Iowa county.

The established clinical and histologic methods of diagnosing genital malignancy were used to determine the efficiency of the vaginal smear as a population screening procedure. The cytologic examination has proved to be of value when used in this manner.

Conclusions

1. Screening of the female population for uterine carcinoma by use of the vaginal smear technique is feasible and valuable provided adequately trained personnel is available.

2. A simplified technique of obtaining a sample of vaginal discharge was devised to adapt the vaginal smear method to population screening.

3. The cytologic method can be used to select those women who need further evaluation by clinical and histologic studies.

4. Each of the methods (cytologic, clinical, and histologic) alone shows an appreciable error rate.

5. It is believed that by coordinating cytologic, clinical, and histologic methods of detection, few genital malignancies will escape detection.

Appendix

All patients treated for genital carcinoma at the University Hospitals are urged to return for examination in three months and every six months thereafter. During the past 18 months a single smear was taken from such patients at each visit. Two hundred forty-four smears were obtained from 197 patients (Table VI), the majority of whom had been treated with x-ray and/or radium. Smear interpretations were compared with the clinical findings, since only 45 patients were subjected to biopsy.

In 47 patients, pelvic examinations showed clinical evidence of residual malignancy or recurrence. The vaginal smears were positive in seventeen, suspicious in seven, and negative in twenty-three. Recurrence was suspected clinically in twenty-seven; this group showed three positive, one suspicious, and twenty-three negative smears. In the remaining 170 with no clinical evidence of malignancy, there were four positive, 19 suspicious, and 147 negative smears.

TABLE VI. CLINICAL AND CYTOLOGIC EVALUATIONS OF 244 SMEARS TAKEN FROM 197 PATIENTS WITH PREVIOUSLY TREATED UTERINE CARCINOMA

PELVIC EXAMINATIONS	VAGINAL SMEAR FINDINGS		
	POS.	SUSP.	NEG.
47 Positive	17	7	23
27 Suspicious	3	1	23
170 Negative	4	19	147

A negative smear is obviously of little significance. However, the presence of abnormal cells correlated very well with the finding of residual carcinoma in the genital tract. In several instances, the recurrence of pelvic malignancy was detected by smears months before it was evident on examination. It is obvious that recurrent genital cancer which is not on a free surface, i.e., deep pelvic tissue extensions, or distant metastases, does not shed cells that can be detected by vaginal smears. It is also possible that the surface of a residual carcinoma may be sealed off by previous radiation. It seems highly probable that vaginal smears will be less satisfactory in evaluating treated carcinomas than in the initial detection of malignancies.

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A STATISTICAL STUDY OF CANCER OF THE CORPUS UTERI

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FROM the inception of this institution as a cancer treatment center in 1913, there have been 957 histologically proved cases of cancer of the corpus uteri admitted to the Roswell Park Memorial Institute up to 1943. These cases were reported in part by Schreiner[1, 2] and by Murphy[3] and represent 21 per cent of the total gynecological admissions, while, during the same thirty-year period, cancer of the cervix represented 65 per cent, carcinoma of the vulva, 3.0, carcinoma of the ovaries 9.0, and malignancies of the tubes and vagina 1.1 per cent of all malignancies of the female genitals. It can be observed from these figures that the ratio of fundus to cervix cancer is slightly over 1:3. This is in agreement with other reports of large numbers of cases in the literature.

Age.—The age distribution of these 957 cases at the time of admission is shown in Table I. A definite peak is noted at the age period 55 to 59 years. The youngest patient was 10 years of age and the oldest 86. The rate of incidence was computed using the female population of New York State, 1940 census, as a standard. These data are also included in Table I and show that the highest incidence is in the age bracket 65 to 69 years. The rates as shown for the various age brackets are not to be considered the actual incidence of fundus carcinoma in the State of New York, since this sample of 957 cases represents only a small portion of all cases of this type in this state.

TABLE I

AGE AT ADMISSION	NUMBER	RATE PER 10,000
10-19	2	
20-24	9	.1517
25-29	4	.065
30-34	14	.236
35-39	26	.462
40-44	42	.791
45-49	84	1.76
50-54	138	3.38
55-59	198	6.21
60-64	184	6.95
65-69	151	7.28
70-74	71	4.95
75-79	29	2.32
80-	5	
Total	957	

Menarche and Menopause.—The distribution of the incidence of menarche reached its highest level at the age of 13 years. The earliest occurred at the age of 8 and the latest at age 22, an apparently normal incidence and distribution.

Seven hundred fifty-four cases, or 78.8 per cent, developed their symptoms subsequent to the menopause, which would indicate that carcinoma of the fundus uteri is predominantly a postmenopausal disease. The natural menopausal age distribution of these cases reached a peak at the age of 50. The average age of menopause, however, is 49.05 years. This is a somewhat later age than that shown by patients with cancer of the cervix and cancer of the vulva, which are 46.3 and 47.1 years, respectively. Also, this is a later average age for the menopause than reported by Fluhmann[4] for a large sample of normal women. The observation of a delayed menopause in this disease has also been reported by Corscaden and Gusberg[5] who reported the peak in his cases at 52 to 54 years and also by Randall[6] who stated that 35 per cent of his fundus cases menstruated after 50 years of age compared with only 8 per cent noncancerous 15 years following the menopause.

Marital Status.—As shown in Table II, there were 105, or 11 per cent, unmarried women among the cases studied. When comparing the various percentages in the different age brackets with the U. S. Census for New York State Rural and Urban population for 1940, there was found to be no significant deviation from that of a standard population. In other words, the ratio of single women to married women is the same as found in a normal population. This figure compares with 11.5 per cent unmarried women as reported by Taylor and Becker,[7] 18.7 per cent as reported by Randall[6] and 24.8 per cent as reported by Corscaden and Gusberg.[5] All of these reports are from clinics in New York State and why there should be such a wide variation in the relative number of unmarried women is not evident. In contrast with these observations on corpus cases, the ratio of single to married women in our cervix cases is definitely less, only 3.8 per cent for the cervix cases and 11.5 per cent for the fundus cases.

A further comparison was made by dividing the married group into two divisions on the basis of term pregnancies, that is, married with no pregnancies and married with no full-term pregnancies. As shown in the lower part of Table II the percentage of women with corpus cancer who comprise this group is significantly greater than the group with cervix cancer. It can be noted from this table that 18.8 per cent of the married women were never pregnant. This figure may be compared with 28.2 per cent as reported by Randall,[6] 31.5 per cent as reported by Taylor and Becker,[7] and 38.6 per cent as reported by Corscaden and Gusberg.[5]

TABLE II. MARITAL STATUS

	CORPUS		CERVIX	
	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
Total	957		500	
Unmarried	105	11.0	19	3.8
	NUMBER	PER CENT OF MARRIED	NUMBER	PER CENT OF MARRIED
Total married	842		481	
No term pregnancies	44	5.2	22	4.57
No pregnancies	159	18.9	56	11.62
	203	24.1 ± 1.47%	78	16.2 ± 1.67%

Weight.—The weight, height, and age of 772 of the 957 patients were available for a comparison with normal weights. The normal for the different height and weight combinations was obtained from Wood.[8] Table III shows that, using the values of Wood as a "norm," 75 per cent of the fundus cases are overweight. For comparative purposes, the deviations from the "norm"

of 180 consecutive cervix malignancy cases are included in this table which shows an overweight for the cervix cases of 62.3 per cent. It is evident that the differences in overweight between the two groups becomes progressively greater with increasing overweight.

TABLE III.

	FUNDUS PER CENT	CERVIX PER CENT
Overweight	75.0	62.3
20 pounds or more	52.9	38.9
40 pounds or more	31.2	18.9
100 pounds or more	4.4	1.1

Nationality.—Several authors have commented on the fact that carcinoma of the fundus is more frequent in Jewish women than carcinoma of the cervix. Corscaden and Gusberg[5] have stated that they found a "proportionate" number of Jewish women among those with cancer of the corpus, and Scheffey et al.[9] in their cases found that carcinoma of the fundus in Jewish women occurred more frequently than carcinoma of the cervix. They give 5.5 per cent occurring in Jews and 3.1 per cent in Negroes. In our group of 957 cases there were only two cases, 0.21 per cent, in Jews and only 3 cases or 0.31 per cent in Negro women. These figures would certainly suggest that corpus cancer is much less frequent in these races.

Diabetes.—The high incidence of coexistent corpus cancer and diabetes has been mentioned repeatedly. Scheffey et al.[9] reported 14 diabetics, or 11 per cent, among 127 cases of corpus cancer. Morse[10] reported a very high incidence of diabetics among his corpus cases; however, he used glucose tolerance tests rather than single fasting blood sugar determinations as the basis for his diabetic diagnosis.

In our 957 cases which cover a thirty-year period, routine blood sugar determinations were not done. In a subsequent group of 165 consecutive corpus cases, however, blood sugar determinations were made and it was found that there were 28 cases, or 16.9 per cent, of the patients who had fasting blood sugars above 120 mg. per cent and this blood sugar level together with glucose tolerance tests, history, and other findings, led to the diagnosis of diabetes.

This figure of 16.9 per cent diabetics has been compared with the results of a diabetic survey by Spiegelman and Marks[11] covering 1,300,399 females. The incidence of diabetes in the general female population over 35 years of age as reported in this survey is 1.02 per cent. Therefore, we find a ratio of diabetes in corpus carcinoma as compared with diabetes in comparable age groups of the general population as a whole to be 16.7 :1.

The high incidence of overweight, late menopause, and sterility would seem to indicate some general endocrine imbalance, further substantiated by the high incidence of associated diabetes. Such an endocrine imbalance is thought to play a role in the etiology of corpus cancer.

Hypertension.—The high incidence of hypertension associated with corpus cancer has been mentioned elsewhere. It is most often mentioned because its presence is a contraindication to surgery. We have studied a large number of recent corpus cases and have found the incidence of hypertension above 140/90 to be 78 per cent. Comparing these findings with a study by Master et al.[12] of more than 6,000 women over 40 years of age, we find that their sample of the general population had hypertension, to the extent of 140/90 in 40 per cent of the cases at ages 40 to 49 and approximately 80 per cent of the cases at age 70 years. Since the majority of our cases fell in the sixth and seventh decades

and our incidence is so nearly that of Master's, we conclude that there is no significant difference in the incidence of hypertension between the corpus cancer cases and their corresponding age-sex group in the general population.

Symptoms.—The most common symptom found in the cases of carcinoma of the fundus uteri was bleeding which occurred in 80.5 per cent of the cases. This symptom is divided into postmenopausal bleeding 63 per cent and intermenstrual bleeding 17 per cent. The second most common symptom was discharge without frank blood which occurred in 15.9 per cent of the cases and pain and pressure symptoms in 4.2 per cent. Comparing the various symptoms, Taylor and Becker[7] found that bleeding as the primary symptom occurred in 96.6 per cent of his cases.

Pathological Classification.—The pathology of the 957 cases of fundus cancer was found to be as follows:

Adenocarcinoma fundus uteri	917 cases
Leiomyosarcoma	31 cases
Squamous cell carcinoma	7 cases
Endometrial sarcoma	3 cases
Deciduoma	2 cases

During this same period there were 121 cases of adenoacanthoma which were classified here as cervix cases, rather than corpus cases. This is contrary to the usual classification as primary corpus cases. Of the 917 cases of adenocarcinoma of the fundus, 786 cases were graded pathologically and are shown in Table IV. The distribution of the pathological grades shows the largest percentage in Grade I and a progressively lower percentage in the following grades. This finding agrees with that of Taylor and Becker[7] who show 63 per cent in their combined grades I and II and 37 per cent in their combined Grades III and IV. For comparative purposes the pathologic grading of 1,134 cases of carcinoma of the uterine cervix are included in Column 2 of Table IV. The distribution of pathology grades in our cervix carcinoma cases is the reverse of that of the fundus cases.

TABLE IV. PATHOLOGIC GRADING

GRADE	CORPUS CASES		CERVIX CASES	
	NO.	PER CENT	NO.	PER CENT
I	321	40.7	127	11.2
II	211	26.8	363	32.0
III	140	17.8	414	36.5
IV	114	14.7	230	20.3

Clinical Classification.—This group of cases has been classified into three stages. Stage I includes those cases in which the disease is confined to the corpus regardless of the size of the uterus. Stage II includes those cases where there is extension beyond the corpus either to the cervix, one or both parametria, vagina, and/or distant metastases. Stage III includes those cases treated elsewhere prior to examination at this institution. These cases had been treated with radium, x-ray, surgery, either subtotal or total hysterectomy, or a combination of these three methods.

Treatment.—It will be noted that the cases herein reported cover a period of 30 years (1913 to 1942 inclusive). It is only natural that there have been numerous changes in the treatment technique and dosage during this period. In the earlier years only low voltage x-rays were available and the supply of radium limited. As a result the dosage from both x-rays and radium was low. Because of the very limited bed capacity of this institution at that period,

practically no surgery for corpus cancer was performed here and only a small percentage of the operable cases were subsequently subjected to surgery elsewhere.

During the next decade, 200 kv. x-ray therapy became available, as well as radon tubes and seeds. Heavier filtration of the intracavitary tubes plus increased penetration of the x-rays resulted in a larger dose to the tumor-bearing area. The x-radiation treatment was of the so-called "massive" dose technique, that is, the entire dose was administered in one or two treatments and as a result the amount of radiation delivered to the tumor was comparatively small.

From 1930 to 1940, radium element intracavitary tubes and fewer radon seeds were used. The average dose delivered by the radium tubes and seeds to a point 2 cm. lateral to the uterine canal was 3,200 rγ and to a point 5 cm. lateral to the canal, 625 rγ. The x-ray technique, too, was altered from the single massive dose to that in which daily increments were delivered over a period of several days. This resulted in increased dosage to the tumor-bearing area, the average x-ray dose being 1,200 r. throughout the pelvis.

During the years 1940, 1941, and 1942, the x-radiation technique changed in two ways: (1) 400 and 1,000 kv. generators were added, making available higher qualities of radiation, 5.0 and 9.0 mm. Cu. half value layer; and (2) a more pronounced protraction of the radiation over longer periods of time, usually several weeks. Thus doses of 3,000 to 4,000 r. were delivered to the tumor area, by means of x-rays alone. When possible, radium intracavitary tubes were introduced delivering doses of 4,000 to 5,000 rγ to the 2 cm. point and 1,000 to 1,400 rγ to the 5 cm. mark. The increase in dosage delivered was possible because the radium content of the individual units had been decreased. It was during this same period, because of hospital expansion, that an increase in surgical intervention took place subsequent to radiation.

In recent years several authors including Heyman,[13] Nolan and Arneson,[14] Martin,[15] and Schmitz[16] have shown improved end results by packing the uterine cavity with radium tubes over the results obtained by utilizing straight tandem tubes. While we have had no experience with this method and cannot compare end results, we do intend using it where surgery cannot be used.

The present procedure in the handling of fundus cancer at this institute is as follows:

Stage I.—Intracavitary tandem radium tubes (1 mm. platinum and 1 mm. steel filtration) are inserted into the uterine canal and left in position until a dose of from 5,400 to 6,700 rγ are delivered to a point 2 cm. lateral to the canal. The tandem tubes are adjusted in length to radiate the entire length of the canal and are filled with radium cells having 1 mg. of radium per ml. length. The time of exposure is usually 100 hours or, in terms of milligram hours, varies from 4,500 to 9,000.

If the case is a suitable risk and the recommendation for surgery is accepted by the patient, a total hysterectomy and bilateral salpingo-oophorectomy are performed six weeks later. If the patient is not suitable for surgery or refuses it, supplementary x-ray treatments are substituted. An endeavor is made in these cases to deliver 3,000 to 4,000 r. into the uterus and broad ligament areas. The combined radium and x-ray dose at a point 2 cm. lateral to the center of the canal varies from 8,400 to 9,700 r., while at 5 cm. lateral to the same point the dose varies between 4,100 and 4,900 r.

Following this type of combined radiation treatment, the patient is examined in three months. If there are persistent symptoms and a repeat diagnostic dilatation and curettage show active tumor cells, additional intracavitary radium treatment is given, approximating two-thirds of the original intracavitary dose.

The persistency of the disease following radiation was investigated in 86 surgical cases. These cases represent all of the Stage I radiated patients who were subsequently operated upon prior to 1948. The latter years were included in order to have as large a sample as possible and were used only to determine the relative number in which the disease was present at the time of operation. Of the 86, 45 were cases admitted between 1943 and 1947 and do not appear elsewhere in this study. Although the intracavitary radium dosage as expressed in milligram hours seems large as compared with the dosages used elsewhere, nevertheless, viable tumor cells were found in 69.7 per cent of the cases at the time of surgery. This compares with 49.6 per cent persistent disease after an average of only 3,600 mc. hr. of intracavitary radium as reported by Taylor and Becker[7] and 75.7 per cent with persistent disease as reported by Corscaden[17] of those cases which have been treated with 1,200 to 5,000 mg. hr. of intrauterine radium.

Stage II.—Since these cases represent the inoperable group a more intensive radiation program is arranged. This consists of radium tubes delivering the same dose as given in Stage I and in addition the same dosage of x-ray as given the nonoperated Stage I cases is delivered immediately upon completion of the radium treatment.

Stage III.—These cases, as stated above, represent secondary or previously treated cases; that is they have been treated elsewhere, by radiation, surgery or a combination of the two methods, prior to admission here. Many have had incomplete or subtotal hysterectomies with a short cervical canal remaining into which a suitable radium container cannot be inserted. Therefore, quite often the treatment in these cases is limited to external irradiation, usually as a palliative procedure. In cases previously treated with radiation only, where there is an adequate canal, the treatment is similar to the radiation given to the primary cases, although the amount of radiation previously administered and the interval between treatments will have a limiting effect on the amount of treatment that can be given safely. Where the disease is still confined to the uterus and where the patient is a suitable surgical risk, we feel that such a patient has a much better chance of survival if a hysterectomy is performed following the secondary radiation treatment. If there is extension beyond the fundus to the cervix or parametria or distant metastases, no surgery will be performed or recommended, and supplemental external radiation will be given in hope of obtaining additional palliation and in rare cases even a clinical cure.

End Results.—The end results of treatment regardless of the method used are presented in Table V. These results cannot be compared satisfactorily with the end results obtained by other clinics because of the difference in clinical classifications. The 32.6 per cent absolute cure rate in Stage III is essentially the same as that of the entire group and would suggest that the treatment given elsewhere, before the initial examination here, coupled with the fact that many of these cases represent recurrent activity of the disease, did not appreciably effect the end results in this stage.

TABLE V. FIVE-YEAR END RESULTS

STAGE	NUMBER ADMITTED	NUMBER TREATED	NO EVIDENCE DISEASE	DIED DISEASE	DIED OTHER CAUSES	LOST	CURE RATE ABSOLUTE PER CENT	CURE RATE RELATIVE PER CENT
I	437	425	189	190	34	12	43.3	44.5
II	225	222	22	185	14	1	9.8	9.9
III	295	274	96	160	8	10	32.6	35.1
Total	957	921	307	535	56	23	32.1	33.3

It seemed advisable, however, to determine the effect on end results of the various changes in methods of treatment instituted throughout the years, as mentioned earlier under the heading *Treatment*. The cases, therefore, were arranged chronologically into the various year brackets. The end results were computed for each bracket based on the number free of disease in relation to the number treated, and are shown in Table VI.

TABLE VI. FIVE-YEAR END RESULTS ARRANGED CHRONOLOGICALLY

YEAR	NUMBER ADMITTED	NUMBER TREATED	NO EVIDENCE DISEASE	DIED DISEASE	DIED OTHER CAUSES	LOST	CURE RATE ABSOLUTE PER CENT	CURE RATE RELATIVE PER CENT
1916-1920	8	7	2	4	0	1	25.0	28.6
1921-1930	182	176	50	109	14	3	27.4	28.4
1931-1939	556	531	172	319	30	10	30.9	32.3
1940-1942	211	207	83	103	12	9	39.3	40.0

From this table it is evident that the end results improved in the more recent years. A slight improvement is shown in the 1931 to 1939 group over that of the 1921 to 1930 group. However, the better end results of the 1940 to 1942 group as compared with the 1931 to 1939 group is more impressive and could be attributed either to improved radiation technique and higher dosages or to the increased utilization of surgical procedures following radiation.

In order to investigate this problem, all Stage I cases from 1934 to 1942 having had surgical intervention subsequent to radiation were compared with Stage I cases having had radiation only. The years 1934 to 1942 were selected because prior to 1934 there were no Stage I cases operated upon in this series, and thus we are enabled to compare the groups for the same period of years. These data are shown in the upper half of Table VII. As can be observed, the nonoperative Stage I cases for the years 1940 to 1942 showed no better end results than for the preceding period. From this we conclude that the greater radiation doses delivered in the latter three years were still inadequate to cope with the disease in a large percentage of the cases.

TABLE VII. ALL STAGE I CASES, 1934-1942

	NUMBER ADMITTED	NUMBER TREATED	5 YEAR NO EVIDENCE DISEASE	DIED DISEASE	DIED OTHER CAUSES	LOST	CURE RATE ABSOLUTE PER CENT	CURE RATE RELATIVE PER CENT
Radiation Only.—								
1934-39	200	192	82	91	15	3	41.0	42.7
1940-42	80	80	33	36	8	3	41.3	41.3
Total	280	272	115	127	23	6	41.1	42.3
Radiation Plus Surgery.—								
Total hysterectomy	30	30	24	4	0	2	80.0	80.0
Subtotal hysterectomy	9	9	3	5	0	1	33.3	33.3
Total surgical cases	39	39	27	9	0	3	69.2	69.2

Comparison of the over-all survival of the operative group with the nonoperative cases indicates that there is a significantly greater survival in the group operated upon. Since the radiation alone was productive of no improvement and since operation subsequent to radiation does show a marked improvement, we conclude that the second procedure is the method of choice.

A further comparison may be made from Table VII. When the group operated upon is divided into two groups according to the type of surgery, whether total hysterectomy with salpingo-oophorectomy or subtotal hysterectomy, the former shows 80 per cent and the latter only 33.3 per cent absolute cure rate, thus further stressing the oft-repeated advice that a total operation should always be performed if possible, and there are very few cases where the total operation cannot be accomplished in Stage I cases.

In a previous publication by two of the authors[18] it was demonstrated that the age of the patient with carcinoma of the cervix uteri was influential in the course of the disease, or in other words that a better prognosis was associated with the more advanced age of the patient. A similar study was made of the fundus cases reported in this paper. All stages of the disease were considered collectively in determining the five-year cure rate in the different age groups. The indeterminate group consisting of all cases who died of other causes, who were lost within the five-year period, or who were not treated here, was eliminated because a comparative study only was being made. The patients were grouped in decades, but due to the small numbers in the early decades the second, third, and fourth decades were considered collectively. Similarly, the last two decades were combined. The results of this comparative study are shown in Table VIII, from which it is evident that contrary to the findings in carcinoma of the cervix, there is a progressively poorer survival with increasing age in carcinoma of the fundus.

TABLE VIII. FIVE-YEAR END RESULTS ACCORDING TO AGE

AGE	NUMBER ADMITTED	NO EVIDENCE DISEASE	DIED DISEASE*	5 YEAR SURVIVAL FREE OF DISEASE PER CENT
10-39	49	30	16	65.2
40-49	109	52	57	47.7
50-59	308	123	185	39.9
60-69	294	90	204	30.6
70-	90	15	75	16.7

*Those cases alive with disease in the fifth year were included with the failures.

Weight, on the other hand, showed no effect on the ultimate results. The survival free of disease for five years was relatively the same for those above and those below a normal weight level.

A comparison was also made on the survival of the married women as compared to the single women. It was found that the survival free of disease for all stages was 32.2 per cent for the single women and 37.0 per cent for the married. This difference, because of the small sample of single women, is without significance.

The response of tumors to treatment is frequently associated with the degree of differentiation of the cells. In Table IX the five-year end results by clinical stages are presented for the combinations of Grade I with II and Grade III with IV. It is evident from this table that the more differentiated tumor group shows a markedly better response to treatment than the more anaplastic group. This was found to be true for all stages of the disease and the cure rates for the two groups differ significantly. This observation is in agreement with Taylor and Becker[7] who showed a cure rate in all clinical groups of 47.2 per cent in pathological Grades I and II combined and 22.8 per cent in pathological Grades III and IV combined. Bowing and Fricke[19] showed a cure rate for all clinical stages of 79.0 per cent for pathological Grade I, 33 per cent for Grade II, 25 per cent for Grade III, and 12 per cent for Grade IV.

Although the pathological grade of the tumor as shown above has a very definite and marked influence on the cure rate in corpus carcinoma, we have been unable to find any such influence of pathological grading on 1,134 cases of cervix carcinoma or on 147 cases of vulvar carcinoma. Smith and Pollack[20] did show some similar influence in their group of vulvar carcinomas, but the number of cases used to substantiate their opinion was too small to make the results significant.

TABLE IX. FIVE-YEAR END RESULTS ACCORDING TO PATHOLOGIC GRADE

	PATHOLOGIC GRADES I AND II				PATHOLOGIC GRADES III AND IV			
CLINICAL STAGE	NUMBER	NO EVIDENCE DISEASE	DIED DISEASE*	SURVIVAL PER CENT	NUMBER	NO EVIDENCE DISEASE	DIED DISEASE*	SURVIVAL PER CENT
I	249	136	113	54.6	104	37	67	35.6
II	119	16	103	13.5	75	2	73	2.7
III	120	50	70	41.6	54	12	42	22.2
Total	488	202	286	41.4 ± 2.23%	233	51	182	21.9 ± 2.71%

*Includes those cases alive with disease in the fifth year.

Discussion of Clinical Classifications

There are so many different clinical classifications in existence, using entirely different criteria, that it is impossible to correlate end results from the different clinics using these various methods of clinical classification, or to evaluate the effect of types of therapy on end results. Our classification has been given earlier in this paper and we are listing below several classifications taken from the literature to illustrate the many factors which various clinics consider important.

Crossen[21]:

Stage I.—The tumor is limited to the surface endometrium and shows no invasion of the muscular layer.

Stage II.—Definite involvement of muscular layers, limited to the inner half of the myometrium.

Stage III.—Extension to the outer half of the myometrium, including possible invasion of the serosa.

Stage IV.—Extension of the tumor outside of the uterus in the parametrium, or the existence of an operable metastatic implant in the ovary.

Stage V.—Extension to adjacent removable organs, verified microscopically.

Stage VI.—Regional extension or distant metastases beyond the scope of surgical removal.

Bowing and Fricke[19]:

Stage I.—The uterus is not enlarged and is freely movable.

Stage II.—Uterus is enlarged but still freely movable.

Stage III.—(a) Uterus is not enlarged but with limited mobility and infiltration of the entire parametrium.

(b) Uterus is enlarged and fixed with infiltration of the entire parametrium out to the pelvic wall.

(c) Uterus is enlarged or not, with involvement of the cervix with or without vaginal invasion.

Stage IV.—Uterus enlarged and fixed; evidence of extrapelvic metastases.

Taylor and Becker[7]:

Stage I.—No enlargement, no extension beyond the fundus.

Stage II.—Enlargement without fixation or metastases:

(a) less than 2½ months' pregnancy in size;

(b) more than 2½ months' pregnancy in size but still freely movable.

Stage III.—Clinical evidence of extension beyond the fundus itself:

(a) extension to cervix only;

(b) extension to vagina, parametrium, adnexae, and distant metastases.

Miller and Henderson[22]:

Stage I.—No palpable enlargement of the uterus.

Stage II.—Moderate enlargement of the uterus to size of 2½ months' pregnancy.

Stage III.—Uterus greater than a three months' pregnancy.

American College of Surgeons:

Primary Cases A. Limited to uterine body.
B. Involvement of broad ligaments.
C. Vaginal metastases.
D. Metastases regional.
E. Metastases remote.

It will be seen from the above that some classifications stress the size of the uterus more than any other factor and indicate that this is more important than extension of the disease beyond the corpus. We cannot agree that this is true. Even if the size of the uterus is as important as some authors indicate, we feel that it is often difficult and sometimes impossible accurately to determine the size of the uterus, since these patients are often extremely obese; even if the uterus is considerably enlarged, it cannot be felt through the obese abdominal wall. We further maintain that the measurement of the uterine canal with a sound will not give accurate indication of the size since the wall of the uterus varies markedly in its thickness and the associated leiomyomas would render this type of measurement inaccurate. We feel that it is often impossible to make a preoperative determination of the size of the uterus accurately enough to state that the uterus is or is not enlarged, and if enlarged whether to the size of a 2½ months' pregnancy or larger. Some of our operative patients have weighed over 300 pounds and many weigh more than 250 pounds.

Crossen[21] has used factors in a clinical classification which obviously cannot be determined clinically, but can be determined only after the uterus has been removed and sectioned. Parts of his classification are obviously worthless in any except operative cases and if preoperative radiation is used it is worthless in these operative cases, since the changes following irradiation are so variable as to be unpredictable.

Three of the above authors, Miller and Henderson,[22] Taylor and Becker,[7] Bowing and Fricke,[19] and others have shown by statistics that the end results are definitely influenced by the pathological grades of the tumors when their entire group of cases is considered for pathological grading only. This paper shows that this belief holds true even when the cases are divided into their clinical groups.

As far as we have been able to determine from the literature, pathological grading has not been used as a factor in classification. This may be because the classification is clinical and pathological grading should not be considered. However, it is felt that anything that has such a definite influence on the end results should be considered in the clinical classification.

Summary

1. Nine hundred fifty-seven cases of corpus cancer are considered and end results are given for the entire group and for each clinical classification.

2. It is definitely shown that total hysterectomy and bilateral salpingo-oophorectomy following preoperative radiation produce the best cure rate.

3. Various clinical classifications are discussed, none of which seems entirely satisfactory and it is thought that some clinical classification employing all of the factors which influence the end results should be adopted, so that the end results from the various clinics could be compared and evaluated.

4. Comments are made on the high incidence of diabetes, overweight, late menopause, and sterility among corpus cancer patients, and the low incidence of corpus cancer among Jewish and Negro women.

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PREGNANCY WITH SICKLE CELL ANEMIA

Review of the Literature and Report of Cases

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WHILE the acute hemolytic crisis of sickle cell disease is not rare, its occurrence in pregnancy has seldom been reported. In a review of the literature, we have found only 23 such cases recorded.[1-14] The review by Kobak, Stein, and Daro[7] is an excellent one. However, several of the cases included appear to be examples of the nonhemolytic form which seems to have little effect on pregnancy.[17] The cases reported since that time[8-14] and the six cases we wish to report bring the total number to twenty-nine. Because of the paucity of recorded material, these are described in detail in order to make available in the literature material for future evaluation.

CASE 1.—(No. 15117). The patient was a nineteen-year-old Negro woman, who had been found to have sickle cell anemia two years before. She had been followed in the Out Patient Clinic, where it was noted she had persistent anemia accompanied by clinical icterus, with icterus indices ranging from 21 to 30 units. Four years before the present hospital admission, the patient had had an abortion at six months' gestation, the cause of which was not known. Three weeks prior to admission, there were weakness and shortness of breath on exertion which became progressively worse, and admission to the hospital was sought. She gave a history of amenorrhea of seven months' duration.

Temperature on admission was 98.6° F., pulse 110, respirations 25, and blood pressure 120/70. Dyspnea was marked, the sclerae were icteric, and there were moist râles in the left lung base. The heart was enlarged to the left with a loud, blowing systolic murmur over the entire precordium. There was uterine enlargement consistent with a pregnancy of seven months' duration. Fetal heart tones were good. There were shallow, punched-out ulcers about both ankles with slight pitting edema of the lower legs.

Laboratory work showed a red blood count of 0.69 million and hemoglobin of less than 7 Gm. per cent (patient died before studies were completed). There was 100 per cent sickling of the red cells at twelve hours. The urine showed a moderate amount of albumin.

Transfusion was started, but when approximately 100 c.c. had been given, she had a severe pyrogenic reaction accompanied by marked dyspnea. The transfusion was discontinued, and she was given morphine sulfate, 10 mg. The lungs were clear to physical examination at the time. Suddenly respirations ceased, and she was pronounced dead two hours after admission. The fetal heart tones were not heard shortly before death.

The blood was retyped and cross-matched several times after death to rule out laboratory error in compatibility.

Necropsy showed 200 c.c. of fluid in each pleural cavity and 250 c.c. of fluid in the pericardial sac. The heart weighed 360 Gm. Its musculature was flabby and pale. There were no abnormalities of the vessels or valves. The lungs showed acute congestion and edema.

The liver was enlarged with accentuation of the vascular pattern. The spleen was a small fibrotic structure, weighing slightly less than 2 Gm. The kidneys showed glomerular engorgement with numerous small red dots in the cortical areas.

Histologic examination showed widespread sickling, the vessels being stuffed with agglutinated masses of these cells which appeared to form actual thrombi, notably in the heart, kidneys, and lungs. The myocardium showed degeneration and possible early necrosis with interstitial and intravascular cellular reaction consisting chiefly of polymorphonuclear leucocytes. There was an erythroblastic hyperplasia of the bone marrow. Extramedullary hematopoietic foci were present in the liver.

Necropsy of the infant which weighed 1,900 Gm. showed no evidence of sickling within the fetal tissues.

CASE 2.—(No. 2603). This sixteen-year-old Negro primigravida came to the Out Patient Clinic six months prior to death. A diagnosis of sickle cell anemia was made, but she declined admission to the hospital. Two months later in the Obstetrical Clinic, she was found to be six months pregnant, and was admitted at this time.

Laboratory data showed a red blood count of 1.75 million, hemoglobin 4 Gm. per cent; white blood count 10,000 with 79 per cent polymorphonuclear leucocytes and 19 per cent lymphocytes. The smear showed 5 per cent nucleated red cells. There was 15 per cent immediate sickling in the sealed wet smear. Van den Bergh reaction was 1 plus indirect. Urinalysis was negative.

Three transfusions of 500 c.c. each were given and the hemoglobin increased from 2 to 6 Gm. per cent, and she was discharged after 32 days to the Out Patient Clinic. Two weeks after discharge, she noticed edema of the ankles which increased rapidly and soon involved the legs and the lower abdominal wall. She was readmitted one month later.

Physical examination showed temperature 100° F., pulse 120, respirations 22, and blood pressure 180/100. There was marked dyspnea and distention of the neck veins. The sclerae were icteric. There were moist râles in both lung bases. The heart was enlarged to the left. The fundus of the uterus was 6 cm. above the umbilicus. Fetal heart tones were audible. There was pitting edema of the legs and thighs.

Laboratory data showed red blood count 1.4 million, hemoglobin 3.7 Gm. per cent, white blood count 36,500 with 75 per cent polymorphonuclear leucocytes, 17 per cent lymphocytes, 6 per cent mononuclears, and 2 per cent eosinophiles. There were many nucleated red cells. Blood urea nitrogen was 17 mg. per cent.

An electrocardiogram showed inversion of P_1 and T_1, low voltage of T_2, T_3, and T_4, findings which were thought compatible with myocardial damage.

She was given 400 c.c. of whole blood intravenously and six hours later she became comatose and failed to respond to stimulants, expiring 20 hours after admission. Since fetal heart tones were not heard during the last four hours, a postmortem section was not done.

Necropsy showed bilateral hydrothorax, hydropericardium, and ascites. The heart weighed 600 Gm. Its ventricular chambers were dilated with flattening of the trabeculae carneae and papillary muscles. The myocardium was flabby and pale. There were no lesions of the valves or coronary arteries. The lungs were acutely congested, with much edema fluid in the lower lobes. The liver, mediastinal, and mesenteric lymph nodes were enlarged. The spleen weighed 95 Gm. The kidneys were swollen and pale. The uterus was enlarged and contained a fetus weighing 1,675 Gm.

Histologically, there was generalized vascular engorgement with variable degrees of sickling throughout the body. Sickling was prominent in the leptomeningeal vessels. Sickle cells were also present in the maternal portion of the placenta. The bone marrow was hyperplastic with increased erythroblastic activity. The spleen was packed with erythrocytes and contained focal areas of fibrosis with deposits of greenish-black pigment. Erythrophagocytosis within the spleen and lymph nodes was evident.

Examination of the fetus showed profound vascular engorgement, but no evidence of sickling.

CASE 3.—(No. 8660) This twenty-two-year-old Negro gravida iii, para ii, was admitted to the hospital with the chief complaint of pain in the legs and chest of two weeks' duration. The past history was noncontributory. Her two previous pregnancies had been normal with spontaneous delivery at term. Both children were alive and well at the time of admission, but were not available for study.

The patient complained of ankle edema, orthopnea, and a painful, nonproductive cough. There was amenorrhea of eight months' duration.

Temperature on admission was 99.6° F., respirations 20, pulse 88, and blood pressure 184/50. The sclerae were icteric. The heart was enlarged to the left with a soft systolic murmur over the precordium. The fundus of the uterus reached the manubrium. There was a 2 plus pitting edema of the ankles as well as pigmented scars on the lower legs.

Laboratory data showed red blood count 2.4 million, hemoglobin 4.5 Gm., white blood count 9,230 with 83 per cent polymorphonuclear leucocytes; the smear showed 6 per cent nucleated red cells. There was 3 per cent immediate sickling with 90 per cent sickling in twelve hours. The urine showed a persistent albuminuria with maximum specific gravity of 1.012. Icterus index 18 units.

The patient was put to bed and given a high vitamin, salt-free diet. She was also given iron and transfused four times with 500 c.c. of whole blood. The blood pressure steadily dropped until it was within normal limits, but the albuminuria persisted. The hemoglobin reached 8.5 Gm. On the twenty-second day, labor was induced with quinine and Pitocin. After an hour of active labor, she spontaneously delivered a term infant in good condition. The postpartum course was uneventful, and the patient was discharged in good condition four days after delivery.

The patient was admitted three years later in the seventh month of pregnancy. She had been seen three months before when her pregnancy was discovered. Her hemoglobin was 8 Gm. and her red cell count was 3.8 million and she had no complaints. She had been examined periodically in the Out Patient Clinic since that time.

When she was admitted she was complaining of intermittent pain in the lumbosacral region. The history was otherwise negative.

Temperature on admission was 98.6° F., respirations 20, pulse 80, and blood pressure 120/75. The sclerae were markedly jaundiced. The heart was enlarged to the left with a blowing systolic murmur heard over the entire precordium. The fundus of the uterus was 27 cm. above the symphysis pubis. The fetus was active and fetal heart tones were good. The remainder of the physical examination was noncontributory.

Laboratory data showed red blood count of 2.34 million, hemoglobin of 2.5 Gm., white blood count of 10,200, with 90 per cent polymorphonuclears, 4 per cent lymphocytes, 6 per cent eosinophiles. There were 30 per cent nucleated red cells, and 9 per cent reticulocytes. There was 15 per cent immediate sickling in the sealed wet smear. The icterus index was 14.4 units. An electrocardiogram showed changes consistent with myocardial damage.

She was digitalized and daily transfusions of 250 c.c. of whole blood were given. After receiving 3,250 c.c. of blood, the hemoglobin increased to only 7.5 Gm. per cent. She was free of symptoms during this period. On the thirteenth hospital day, her temperature suddenly rose to 104° F. The sclerae appeared more icteric, but physical examination was otherwise negative. The white blood count was 28,000 with 92 per cent polymorphonuclears, and 2 per cent nucleated red cells. The hemoglobin was 7.5 Gm. per cent. Icterus index was found to be 42 units. The urine showed 4 plus albuminuria with a moderate number of granular casts. X-ray of the chest was negative. The next afternoon the patient complained of slight pain in the left lower quadrant, and one hour later spontaneously delivered a premature female infant in good condition. The elevated temperature continued. The icterus index reached 57 units, and the blood urea nitrogen 90 mg. per cent. However, the urinary output remained over 1,000 c.c. in twenty-four hours. On the first postpartum day the respirations increased to 40 per minute and crackling râles were noted in the right base. The icterus index had risen to 176 units and the hemoglobin had dropped to 4.5 Gm. per cent. She

pursued a steady downhill course with respirations increasing to 60 per minute, and the pulse to 130. Terminally the pulse and respiration seemed to cease at almost the same instant. Death occurred early in the morning of the second postpartum day, or on the seventeenth hospital day. Permission for necropsy could not be obtained.

The red cells of the child were examined, and 3 per cent sickling was found in twenty-four hours.

CASE 4.—(No. 42802). This twenty-five-year-old multigravida had been twice previously delivered in the hospital. On her first admission she was a primigravida in early labor. Hemoglobin at this time was 7.5 Gm., and the icterus index 25 units. There was 85 per cent sickling of the red cells in 24 hours. She received a transfusion of 500 c.c. of whole blood. After thirty-seven hours of labor, delivery was effected by midforceps. There was puerperal morbidity of five days' duration, during which she received two more transfusions of 500 c.c. each. She and the infant were discharged in good condition on the tenth postpartum day.

On her second admission she was in active labor. The prenatal course had been uneventful. There had been no fetal movements for the past twelve hours, and no fetal heart tones were heard on physical examination. Hemoglobin was 7.5 Gm., sickling was again present. After sixteen hours of labor she delivered a stillborn, macerated infant with cord wrapped tightly around its neck. She was given one transfusion before discharge.

Between her second and third admissions, she delivered a normal, full-term infant in her home.

She was admitted for the third time four hours after spontaneously delivering a full-term infant in good condition, in her home, attended by the Out Patient Service. The patient had attended clinic infrequently in spite of frequent promptings. She did not follow instructions and refused admission even for delivery. She complained of weakness, fatigue, and difficnulty in breathing.

On admission, temperature was 99.6° F., pulse 120, respirations 30, and blood pressure 104/70. Dyspnea was marked. There was a blowing systolic murmur at the apex.| The fundus of the uterus was firm and at the level of the umbilicus.

Laboratory data showed a red blood count of .9 million, hemoglobin of 2.4 Gm., white blood count 20,000 with 92 per cent polymorphonuclears. The icterus index was 14.7 units. There was 1 per cent immediate sickling with 100 per cent sickling in forty-eight hours. Blood work was repeated after three transfusions and showed a red blood count of 2.1 million and hemoglobin of 5.07 Gm. The urine was negative.

Transfusion of 500 c.c. of whole blood was given shortly after admission and the dyspnea was completely relieved. Transfusions were given on the first and second days of the hospital stay, but not on the third day. She received another transfusion on the morning of the fourth hospital day. Late that afternoon the patient developed acute pulmonary congestion and some ankle edema. She was digitalized and given oxygen by nasal catheter. There was little response, and the patient expired seven hours after onset of the symptoms. Permission for necropsy was not granted.

The infant was found to have a red blood count of 5.8 million with a hemoglobin of 15 Gm. There was no sickling. He took nourishment well, gained weight rapidly, and was discharged in good condition.

CASE 5.—(No. 11970). This seventeen-year-old gravida i was first admitted to the hospital in 1944 in labor. She had been followed in the Obstetrical Clinic and was found to have persistent anemia, the etiology of which was undetermined at that time: Her past history was essentially negative.

Temperature on admission was 99.6° F., pulse 100, respirations 16, and blood pressure 132/82. There was a systolic murmur at the apex. Fetal heart tones were good.

Laboratory data showed a red blood count of 2.7 million, hemoglobin 5 Gm., white blood count 20,000 with 67 per cent polymorphonuclears. The reticulocyte count was 15 per cent.

Icterus index was 27 per cent. There was 75 per cent sickling in forty-eight hours. Repeated urinalyses showed a persistent albuminuria, the highest specific gravity recorded being 1.013.

After a twenty-seven-hour labor, the patient spontaneously delivered a full-term infant in good condition. There was puerperal morbidity for two days. The postpartum course was otherwise normal, and she was discharged in good condition on the seventeenth postpartum day.

She was again admitted three years after her first admission, in labor. The three years between admissions had been uneventful. The patient was seen on two occasions in the Prenatal Clinic. In the sixth month her hemoglobin was 8 Gm. and in the seventh month 5 Gm. She did not return to the Prenatal Clinic again.

On admission, temperature was 100.6° F., pulse 120, respirations 20, and blood pressure 125/80. There was a systolic murmur over the entire precordium. The uterus was the size of a term pregnancy. The fetal heart tones were good. Uterine contractions were irregular and there was no cervical dilatation.

Laboratory data showed red blood count of 0.9 million, hemoglobin 3 Gm., white blood count 18,525 with 92 per cent polymorphonuclears; the smear showed 5 per cent nucleated red blood cells. There was 1 per cent immediate sickling with 100 per cent sickling in forty-eight hours. Icterus index was 18 units.

The patient was in false labor. She was given four transfusions, and the hemoglobin reached 5.5 Gm. On the ninth hospital day, labor was induced by rupture of the membranes. A normal infant was delivered. Postpartum course was uneventful, and the patient was discharged in fair condition on the twentieth postpartum day.

CASE 6.—(No. 62685). This nineteen-year-old gravida ii was first seen in the Out Patient Clinic two weeks prior to admission, complaining of tingling and numbness in the fingers and toes, headaches, and epistaxis of one week's duration. On admission to the hospital, these symptoms had ceased, but she was complaining of general weakness and pain under the left breast and severe pain in both shoulders, the neck, and upper dorsal spine. She had been in bed since her last clinic visit. Her first pregnancy had resulted in an abortion at six months, otherwise her past history was one of good health.

On physical examination, temperature was found to be 98.6° F., pulse 84, respirations 16, and blood pressure 132/82. She was an acutely ill, emaciated Negro woman with an intrauterine pregnancy of approximately seven months. Fetal heart tones were good. There were definite neck rigidity, tenderness to palpation across the shoulder girdle and along the entire length of the spine. Reflexes were physiological. There was a soft murmur over the entire precordium. Physical examination was otherwise negative.

Laboratory data on admission and throughout her hospital stay are shown for the most part in Fig. 1. There was 5 per cent immediate sickling and 90 per cent sickling in twenty-four hours. Urinalysis was negative. Repeated examinations showed a negative spinal fluid except that proteins were persistently above 100 mg. X-rays of the skull, spine, and chest were negative. Electrocardiograms showed sinus arrhythmia. Mantoux, Wassermann, and Kline tests were negative. A Frei test showed a 2 plus reaction.

Symptomatic and supportive therapy were given in the form of high-calorie, high-vitamin diet, iron medication, and anodynes. She was confined to bed during the greater part of her hospital stay. There were frequent exacerbations of her symptoms, but the neck rigidity and tenderness persisted. Weakness and inability to move about without discomfort were marked. The pregnancy apparently proceeded normally with no suggestion of premature labor or fetal difficulty. Ten days before her estimated date of confinement, labor began spontaneously. After thirty-six hours, the patient spontaneously delivered a 5 pound, 7 ounce infant in good condition. Increased blood destruction during the course of labor was shown by a series of icterus indices at four-hour intervals, the highest titer being 33 units. The postpartum course was uneventful. All symptoms ceased, and the neck rigidity disappeared shortly after delivery. The patient was up and about the ward on the fourth

postpartum day, complaining only of slight weakness. She was discharged in good condition on the tenth postpartum day.

The infant showed no evidence of sickling in a series of sealed wet smears.

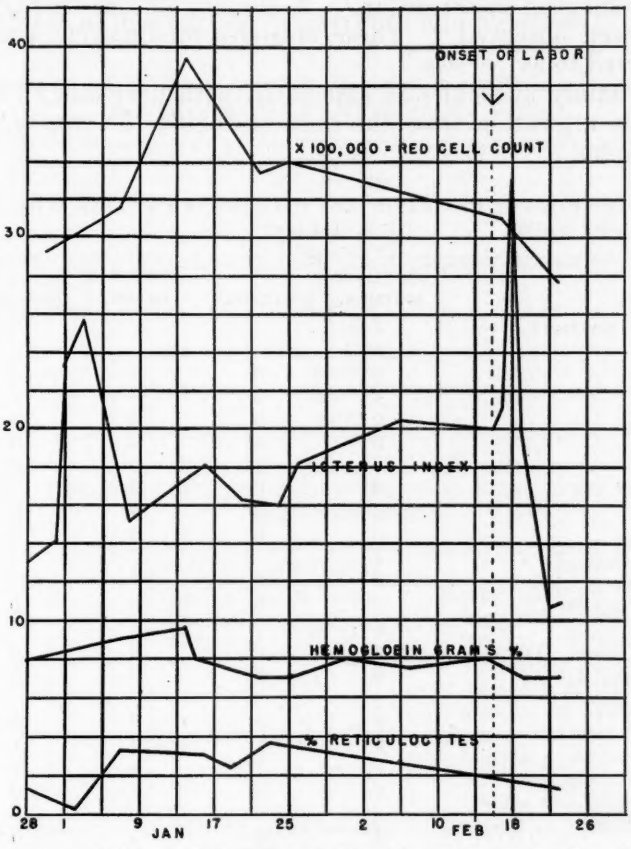

Fig. 1.—Graphic representation of laboratory findings in Case 6, showing sharp rise of icterus index with onset of labor.

Discussion

Sickling of the red blood cells is an hereditary abnormality found in 7 to 14 per cent of American Negroes.[15, 16, 17] It is transmitted as a dominant Mendelian factor.[18, 19, 20] There are two forms of sickle cell disease: (1) sicklemia in which there is sickling of the cells, but no evidence of blood destruction or increased rate of regeneration and (2) sickle cell anemia in which there is not only sickling, but also active blood destruction and such evidence of increased regeneration as reticulocytosis and nucleated red cells. The ratio of sickle cell anemia to sicklemia has been estimated as from 1:9 to 1:40.[15, 21]

The relationship of the two forms is not clear. Some individuals with the trait are known to go through life without ever showing the anemia. However, if the active form develops, it usually begins in the first two decades of life and once the blood destructive process is activated it does not disappear. Wintrobe[22] reports that he has observed remissions, but never to the extent that there was no evidence of blood destruction.

From time to time, the blood destructive process appears to be accelerated and may be accompanied by episodes of aching and pain in the joints or extremities. There may be severe abdominal pain with accompanying prostration and muscular rigidity closely simulating one of the acute abdominal accidents requiring surgical intervention.[22] A clinical picture simulating coronary occlusion has been observed.[23] These episodes of apparent acceleration are sometimes referred to as "crises."

A previous study of sicklemia associated with pregnancy[17] indicates that it produces little alteration from the normal during the course of pregnancy and the puerperium.

TABLE I. COMPLICATIONS OF PREGNANCY AND DELIVERY IN PATIENTS WITH SICKLE CELL ANEMIA

CASE	DEATH OF MOTHER	STILLBORN	PREMATURE LABOR	TOXEMIA	MORBIDITY
1. Fouché and Switzer‡	+				
2. ‡	+			+	
3. (A)	0	0	0	+	
(B)	+	0	+	+	+
4. (A)	0	0	0	0	+
(B)	0	+	0	0	0
(C)	+	0	0	0	0
5. (A)	0	0	0	+	+
(B)	0	0	+	0	0
6.	0	0	0	0	0
7. Yater & Mollari (1)*	+				
8. Richter, et al. (2)	0	0	0	0	+
9. Sharp & Schleicher (3)	0	0	0	0	0
10. Lewis (4)*	0				
11. Sodeman & Burch (5)	0	0	0	0	0
12. Page & Silton (6)	0	0	0	0	0
13. ‡	+				
14. Kobak, et al (7)	+	+	0	0	0
15.	0	+	0	+	0
16.	0	0	+	+	+
17.	0	0	0	0	+
18. Van der Sar (8) (A)	0	+	+	0	0
(B)	0	0	0	0	0
19. Spivak (9)	0	0	0	+	0
20. Zimring (10)†	0	0	0	0	+
21. Noyes (11)‡	+			+	0
22. Martinak (12)†	0	0	0	0	+
23. Hodges & Bernstine (13)	0	0	+	+	0
24. (A)	0	0	0	0	0
(B)	0	0	+	0	0
25.	0	0	0	0	0
26. Carangelo & Otts (14)	+	0	+	0	+
27. (A)	0	0	0	0	0
(B)	0	0	0	0	0
28.	0	0	0	0	0
29.	0	+	0	0	0

*Case 7 aborted spontaneously at 6 months. Case 10 was aborted therapeutically.
†In Cases 20 and 22 there was postpartum hemorrhage.
‡Died undelivered.

In a review of the literature, reports of only 23 definite instances of sickle cell anemia associated with pregnancy were found. All cases were excluded which did not show clinical or laboratory evidence of jaundice in addition to the sickling trait. In most accepted instances, there were also reported an increased reticulocyte count and the finding of normoblasts or other nucleated erythrocytes in the circulating blood, important presumptive evidences of a blood destructive type of anemia.

Complications of pregnancy and delivery in the 29 patients available for study have been summarized in Table I.

As shown in Table II, there is an increase in the incidence of major complications of pregnancy and labor in patients who have sickle cell anemia with the exception of postpartum hemorrhage and abortion.

TABLE II. INCIDENCE OF COMPLICATIONS OF PREGNANCY IN SICKLE CELL ANEMIA PATIENTS AS COMPARED WITH OTHER GRAVID WOMEN

	AVERAGE AS REPORTED IN STANDARD TEXTS (PER CENT)	SICKLE CELL ANEMIA PATIENTS (PER CENT)
Anemia (hemoglobin)	66[24]	37.4
Postpartum hemorrhage	5-7[25, 26]	5.5
Premature labor	2.95[27]	19.4
Stillbirths	2.41[28]	13.8
Morbidity	10.5[28]	25
Abortion	20[28]	10.8
Toxemia	10[28]	25

TABLE III. REPORTED CAUSE OF DEATH IN PATIENTS WITH SICKLE CELL ANEMIA AND PREGNANCY

CASE	CLINICAL IMPRESSION	AUTOPSY FINDINGS
1. Fouché and Switzer	Transfusion reaction; congestive heart failure	Marked sickling. Pericardial effusion, myocardial dilatation and hypertrophy. Myocardial degeneration, congestion of lungs, hepatomegaly. Atrophy of spleen. Passive congestion of liver and kidneys.
2. Fouché and Switzer	Congestive heart failure	Marked sickling, generalized edema, bilateral hydrothorax, hydropericardium, ascites. Cardiac hypertrophy and dilation, enlarged liver.
3. Fouché and Switzer	Sickle cell crisis bronchopneumonia	Autopsy not obtained.
4. Fouché and Switzer	Congestive heart failure	Autopsy not obtained.
7. Yater and Mollari[1]	So-called abdominal crisis—thrombosis of hepatic arteries?	Enlarged liver, hydroperitoneum, hydropericardium, heart dilated, hypertrophied, atrophy of spleen, old infarcts of spleen and kidney.
13. Page and Silton[6]	Bronchopneumonia; anemia	Hemorrhagic infarcts in lungs; early bronchopneumonia, pelvic phlebothrombosis
14. Kobak, et al.[7]	Pneumonia	Marked sickling, enlarged liver and spleen. Myocardial degeneration. Atelectasis of lungs. Passive congestion of liver, spleen, and kidneys.
21. Noyes[11]	Congestive heart failure. Toxemia of pregnancy.	Marked sickling. Right-sided heart failure, pleural effusion, visceral congestion.
25. Carangelo and Otts[14]	Overwhelming renal infection	Bilateral medullary abscesses of both kidneys. Severe icterus.

The increase in morbidity is best explained by the decreased resistance of these patients to infections because of the severe anemia. However, it must be remembered that in sickle cell anemia spontaneous thrombosis and infarction are frequent with subsequent fever and leucocytosis. The cause of

the increased incidence of premature labor and stillbirths is obscure. Thrombotic phenomena often occur in other parts of the body in sickle cell anemia and may well occur in the fetal or maternal portion of the placenta, thereby precipitating these events. An explanation for the increased incidence of toxemia of pregnancy in these patients is likewise difficult to find. Renal damage may be suspected as being a factor in some instances.

In Table III it is shown that the most common cause of death in sickle cell anemia complicated by pregnancy is congestive heart failure.

The mortality, 31 per cent in these patients, is large and even though the prognosis for long life in the patient with uncomplicated sickle cell anemia is not good,[7, 22] it indicates that pregnancy is a severe additional strain.

Fig. 1 is a graphic representation of certain laboratory findings in Case 6. It indicates that the blood destructive process was accelerated with the onset of labor in this patient. There are no other studies available which would indicate that the onset of labor causes increased blood destruction in the patient with sickle cell anemia. Pregnancy itself does not seem to precipitate an active form of sickle cell disease in sicklemic women,[17] although 55 per cent of the reported cases of sickle cell anemia with pregnancy are in primiparas who give no history of previous blood destructive episodes. It is possible that a previously mild but active form of the disease which had been unnoticed becomes symptomatic in the presence of the added burden of pregnancy.

Sickling was observed in 5 of 16 children of mothers with sickle cell anemia, or 31 per cent of those examined in the course of the observations made by the various groups whose data we have analyzed in Table I.

The treatment of the patient with sickle cell anemia is unsatisfactory. There is no specific therapy. The use of iron, vitamins, and protein apparently influences the disease slightly if at all. The treatment that we consider most useful in the sickle cell patient with pregnancy is outlined in the following paragraphs.

A. *In Crisis.*—Multiple transfusions will provide a temporary supply of blood. This is directed primarily toward correction of the anemia and the relief of attendant symptoms. Because of the tendency of patients with sickle cell anemia to have reactions to transfusions[22] and to go into congestive heart failure, the blood must be given very slowly. It is probably wise to alkalinize the patient's urine beforehand. It is also recommended that the blood be given in small quantities and at more frequent intervals than the usual 500 c.c. transfusion. Since the cause of death in these patients is so often a sudden onset of congestive heart failure, we believe that prophylactic digitalization is indicated.

B. *Not in Crisis.*—The use of multiple blood transfusions throughout the last trimester and before the onset of labor has been recommended by Spivak.[9]

1. In light of the present knowledge concerning the reaction of sickle cell anemia patients to operative procedures, it is questionable in our minds as to which is the procedure of choice: (a) termination of pregnancy by therapeutic abortion or (b) attempting to carry the patients to the stage of fetal viability. Since these patients do seem to have at least a temporary improvement once they are delivered, induction of labor as soon as the fetus is viable may be advisable. If the patient with a past history of hemolytic crises is seen in the early stages of pregnancy and the disease is in the inactive or latent phase, therapeutic abortion should be seriously considered.

2. A decrease in oxygen tension causes an increase in sickling of the red blood cells[30] with increased viscosity and possibly localized or generalized

stasis.[31, 32] Therefore, local anesthesia would be the anesthetic of choice, or an inhalation anesthetic with a high oxygen proportion.

3. Prophylactic digitalization might well be employed routinely in these patients prior to any operative procedure.

Summary

The twenty-three reported cases of sickle cell anemia complicating pregnancy have been reviewed. Six additional cases are reported and tentative recommendations as to therapy have been made.

Conclusions

1. Sickle cell anemia is a serious complication of pregnancy. The prognosis for both mother and child is very grave.

2. Toxemia of pregnancy, premature labor, morbidity, and mortality are definitely increased in these patients.

3. The treatment of a patient in the active phase or crisis stage is unsatisfactory. Prophylactic digitalization is indicated.

4. Treatment of the patient in the latent phase should consist of prophylactic digitalization and induction of labor as soon as viability of the fetus is established.

5. Patients with known sickle cell anemia who are not pregnant should have therapeutic sterilization or use adequate contraceptive measures.

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THE ATTITUDE OF THE FETUS IN BREECH PRESENTATION

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IN RECENT years, the trend toward reduction in the maternal and fetal mortality has been quite marked. However, the fetal mortality rate in breech deliveries is much too high. This study is made to determine the results of the management of breech deliveries since the opening of the Woman's Clinic of the New York Hospital in 1932. By reviewing the data collected on breech deliveries, we hope that some conclusions can be drawn that may direct us to better management and lead to a reduction in the fetal mortality rate of breech deliveries. In a search for more information concerning this problem, the x-ray was utilized to determine what influence the attitude of the fetus *in utero* had upon the mechanism of labor in breech deliveries.

Otto Brakemann, in 1936, reported the results of a similar radiological survey. His series was not conclusive but he gained the impression that, in breech presentation, with the vertex in a deflexed attitude, more difficulty in labor resulted. Also, he felt that such deliveries necessitated operative procedures more frequently. It was of interest to note whether the information from our x-ray files substantiated his theory, and if so, how such information could be used to better practical advantage.

Incidence of Breech Presentation

From Sept. 1, 1932, to Dec. 31, 1947, there were 45,837 full-term and premature deliveries in the Woman's Clinic of the New York Hospital. Of this number, there were 1,918 full-term and premature breech deliveries. Our incidence of breech presentation, therefore, is 4.2 per cent, which compares very closely to other large series reported in the literature. (Heaton, Tompkins, and Martius reported an incidence of 4.6, 4.7, and 3.4 per cent, respectively) Martius, excluding all premature infants and twins, found the incidence of breech presentation to be 2.5 per cent of full-term single pregnancy deliveries. Hecker, whom Martius quotes in Halban and Seitz, found an incidence of 3.2 per cent of all births. Of the breech deliveries he studied, 74.5 per cent were frank breech presentations and 24.5 per cent full breech presentations. He also stated that one per cent of them presented with a knee.

In the Woman's Clinic of the New York Hospital, 54.93 per cent of patients with breech presentations were primiparas, 45.07 per cent multiparas. There were 91 cesarean sections done, an incidence of 4.7 per cent. This is slightly higher than the incidence of 3 to 4.5 per cent for cesarean sections in all deliveries at the Clinic.

Etiology of Breech Presentation

There are many theories concerning the etiology of breech presentation. The principal factors that are discussed in the literature are: pelvic contractions,

abnormalities of the fetal head, abnormalities of the uterus, prematurity, hydramnios, and hereditary tendencies.

Pendleton Tompkins, after reviewing the causes of breech presentation, concluded that the so-called "classic" causes accounted for only 6 per cent of the cases. He does not feel that a contracted pelvis could be considered a cause, since in 89 per cent of his cases there was no evidence of contraction.

Many of the patients with breech presentation had a radiological examination of the maternal pelvis. The data obtained from these films and that obtained from clinical examinations of the pelves revealed that in 87.1 per cent of our cases of breech presentation the pelves were normal.

A comparable number of patients with infants presenting by vertex was studied, choosing at random the cross-section year 1943. Of 3,017 deliveries recorded, normal pelves were encountered in 89.2 per cent. From these data it would appear that contraction of the pelvis is not an etiological factor in breech presentation.

Fetal Mortality

Martius, at the University of Bonn, found the fetal mortality in breech deliveries to be 14 per cent. Goethals, in Boston, reported in 1936 that the crude fetal mortality figures in uncomplicated breech deliveries for primiparas with a single pregnancy were 18.1 per cent; multiparas with a single pregnancy, 17.2 per cent. After macerated and badly malformed babies were excluded, the corrected mortality rate was 13.6 per cent, subdivided as follows: premature infants, 53.6 per cent mortality; immature infants, 10.0 per cent mortality. The mature babies had a 6.9 per cent fetal mortality, representing the risk in uncomplicated deliveries with a mature baby. Dieckmann reported the gross fetal mortality of term babies to be 7.7 per cent. His premature infants had a 25+ per cent fetal mortality. Causes of death were: prematurity, intracranial injury, asphyxia, and a small number of visceral lesions.

In our series (as shown in Table I) there is a total of 1,660 full-term and premature deliveries with 200 deaths. Note that the multiparas have a higher fetal mortality rate than the primiparas. The total gross fetal mortality rate is 12 per cent. The cause for the increased rate in multiparous patients is not clear. Goethals found that mature babies of multiparous patients suffered a greater risk than those of primiparas. He investigated the possibility that multiparas are more likely to give birth to large and overdeveloped infants. However, in his series, it was found that the fetal mortality rate was lower in the large (8 pounds plus) babies of multiparas compared with the large one of primiparas. There was a higher percentage of large babies in multiparas in the series reported by Goethals.

TABLE I. INFANTILE MORTALITY IN BREECH PRESENTATION

	SPONTANEOUS DELIVERIES			OPERATIVE DELIVERIES			TOTAL		
	NO. CASES	INFANT DEATHS	PER CENT	NO. CASES	INFANT DEATHS	PER CENT	NO. CASES	INFANT DEATHS	PER CENT
Primiparas	29	5	17.2	883	84	9.5	912	89	9.8
Multiparas	72	15	20.8	676	96	14.2	748	111	14.8
Grand total	101	20	19.8	1,559	180	11.5	1,660	200	12.0

The cause of fetal death was checked in our 200 cases and the etiological factors rank in the following order: Prematurity, 31 per cent; congenital anomalies, 19 per cent; intrauterine asphyxia incident to delivery, 10 per cent; prolapsed cord or cord tight about the neck, 9 per cent; intrauterine infection,

9 per cent; intracranial hemorrhage, 8 per cent; premature separation of the placenta and placenta previa, 5 per cent; and, in the other 9 per cent, the cause was dubiously syphilis, hemorrhagic disease, or was undetermined. But eliminating prematurity and congenital anomalies, the corrected fetal mortality is 6.0 per cent. There was no obvious difference between multiparas and primiparas when the cause of death in each group was analyzed, except for the deaths that occurred due to prolapse of the cord. Such accidents were responsible for 14 per cent of the fetal deaths in multiparas, but for only 6 per cent of the fetal deaths in primiparas. It is suggested that the multiparous patient may suddenly become fully dilated much more frequently than the primiparous patient. A prolapsed cord might be undetected in such cases until asphxia of the fetus has occurred. The number of excessive-sized infants (4,000 Gm. or over) was statistically the same in each group. The number of premature deaths in each group revealed no significant statistical difference.

In Table I we have compared the fetal mortality rate in spontaneous deliveries with that in operative deliveries. There is a preponderance of operative deliveries. In the accumulated data of the Clinic, a breech delivery is classified as a breech extraction and thus an operative delivery if even so much as a Mauriceau-Smellie-Veit maneuver is necessary. If forceps are used on the aftercoming head, it of course is classified as an operative delivery. The mortality rate for the fetus is higher in spontaneous than in operative deliveries, 19.8 per cent and 11.5 per cent, respectively. However, premature infants are more likely to have a spontaneous delivery.

The operative deliveries have been subdivided in the manner shown in Table II. There is little difference in the fetal mortality when the breech extraction deliveries are compared with those in which the forceps were used on the aftercoming head. When cesarean section was done, the fetal mortality dropped significantly to 4 per cent. The fetal death in each cesarean section case was caused by abruptio placenta. In view of the lesser fetal risk with the employment of abdominal delivery, it has been the policy of this Clinic to do a cesarean section on most elderly primiparas at term with a breech presentation. The result has been very gratifying.

TABLE II. INFANTILE MORTALITY IN BREECH PRESENTATION BY TYPES OF OPERATIVE DELIVERY

	PRIMIPARAS			MULTIPARAS			TOTAL		
	NO. CASES	INFANT DEATHS	PER CENT	NO. CASES	INFANT DEATHS	PER CENT	NO. CASES	INFANT DEATHS	PER CENT
Breech extraction	641	63	9.9	583	88	15.1	1,224	151	12.3
Forceps on aftercoming head	191	19	9.9	51	6	11.8	242	25	10.3
Cesarean section	50	2	4.0	40	2	5.0	90	4	4.4

Maternal Mortality

In our series of 1,918 breech deliveries, six maternal deaths were noted. The maternal mortality rate in breech deliveries is 0.31 per cent, or 3.1 per thousand cases. The diagnosis in each case is: hemorrhage, 2 cases; acute yellow atrophy of the liver, 1 case; and puerperal infection with peritonitis, 3 cases.

Radiological Survey

An attempt has been made to evaluate radiological studies of the fetus in breech presentation. Brakemann's impression that operative interference is necessary most commonly in the cases showing an extended attitude of the fetus is challenged in this study. A comparable number of cases are reported and the clinical result noted in each case.

Brakemann (Table III) did not indicate the exact data concerning the course of labor and delivery in his cases. He merely stated that a more difficult labor and delivery was noted in those having a deflexed attitude of the vertex.

TABLE III. RADIOLOGICAL SURVEY OF FETAL ATTITUDE IN BREECH PRESENTATION
(From Brakemann, Otto: Ztschr. f. Geburtsh u. Gynäk. 112: 154, 1936.
191 Cases of X-ray Examination With Fetus in Utero)

ATTITUDE OF VERTEX	NUMBER CASES	PER CENT
Complete flexion	42	21.9
Neutral (middle)	116	60.7
Mild extension (sinciput)	12	6.2
Forehead extension	19	9.9
Face extension	2	1.0
Total	191	99.7

In the data collected at the Woman's Clinic of the New York Hospital (Table IV) 216 cases were reviewed. In all of these, an abdominal flat plate was made and in many a pelvic radiological examination. Again, as shown in the data of Brakemann, the deflexed, neutral, or military attitude was most frequently encountered. In all cases that had deflexion of the vertex beyond the neutral or military attitude, the term hyperextension is used. Emphasis should be placed, we think, on the fact that the most common attitude for the head to assume is that of neutral or the so-called "military." The comparable figures in this series and that of Brakemann would seem to be statistically correct.

TABLE IV. RADIOLOGICAL SURVEY OF FETAL ATTITUDE IN BREECH PRESENTATION

ATTITUDE OF VERTEX	NO. CASES	PER CENT
Complete flexion	86	39.8
Neutral extension (Middle, military)	107	49.5
Hyperextension (Sinciput, forehead, face)	23	10.7
Total	216	100.0

In the mechanism of labor of breeches, the important feature of the fetal attitude is that of the relationship of the vertex to the spine. It is postulated that the forces of labor are exerted by the fundus of the uterus upon the vertex and transmitted through the fetal spine to the presenting part. Such an action causes descent and engagement of the breech. Another factor in causing descent is the straightening out of the spine and body of the fetus. Thus it would seem that the neutral or military attitude of the vertex and spine would be the most favorable. The data concerning the relationship of the vertex to the spine are tabulated in Table V. The interpretation of the degree of deflexion of the spine is subject to a certain amount of error due to individual interpretation of the films. Only in the cases with *hyperextension of the vertex* did one see *hyperextension of the spine.*

TABLE V. RELATIONSHIP OF VERTEX TO SPINE OF FETUS IN BREECH PRESENTATION

ATTITUDE OF VERTEX	NUMBER CASES	ATTITUDE OF SPINE		
		FLEXED	EXTENDED	HYPEREXTENDED
Flexed	86	85	1	0
Extended	107	96	11	0
Hyperextended	23	1	11	11
Total	216	182	23	11

It is commonly taught that the duration of labor with breech presentations is prolonged. This problem was investigated in the 216 cases subjected to the

radiological survey; 160 of these delivered vaginally, and 28 by means of cesarean section. The remaining cases were not considered suitable for analysis. In Table VI, the duration of labor in the 160 vaginal breech deliveries is tabulated. The data are most favorable in the 80 cases which had an extended (neutral or military) attitude of the vertex in utero. In this group, 73.8 per cent had labors lasting eighteen hours or less. Since it is taught that the duration of labor in all deliveries of primiparas is normally eighteen hours (twelve hours in multiparas), it would seem logical to compare the duration of labor in breech deliveries to this eighteen-hour figure. The median duration of labor in the flexed, extended, and hyperextended heads was seventeen, thirteen, and eighteen hours, respectively. In our data for the 1,660 full-term and premature breech deliveries, the median duration of labor was found to be eleven hours. In 1943 (a cross-section year chosen at random), there were 3,116 deliveries with the fetus presenting by the vertex, and the median duration of labor in this group was found to be ten hours. We realize that the small series of 160 cases is hardly comparable to 1,660 cases.

TABLE VI. BREECH DELIVERIES. DURATION OF LABOR IN VAGINAL DELIVERIES

HOURS OF LABOR	ATTITUDE OF VERTEX						TOTAL	
	FLEXED		EXTENDED		HYPEREXTENDED			
	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
1-18	36	59.0	59	73.8	10	52.6	105	65.6
19-35	15	24.6	12	15.0	6	31.6	33	20.6
36-50	7	11.5	3	3.7	1	5.3	11	6.9
50 plus	3	4.9	6	7.5	2	10.5	11	6.9
Total	61	100.0	80	100.0	19	100.0	160	100.0

In order to learn more about the mechanism of labor, many of our films were taken after the onset of labor. Some were rechecked in the first stage and others were checked in the second stage of labor. Two were taken with the breech on the perineum. Fig. 1 is just such an example. It is to be noted that the vertex is *neutrally* placed and the spine is fairly straight with some slight degree of flexion in it. The arms are in front and flexed. This case resulted in a very easy assisted breech delivery. The neutral status of the vertex is most commonly encountered, and it is here demonstrated that the neutral status of the vertex is maintained in the second stage of labor just prior to engagement of the aftercoming head in the pelvis.

In comparison, we have an x-ray (Fig. 2) showing the fetus with marked *hyperextension* of the vertex and spine. Note that the face of the fetus is looking up and there is a sharp angulation of the neck; the remaining portion of the spine is straight but not hyperextended. It would appear that the fetus needed more room in utero. The maternal pelvis in this case was normal. Due to prolapse of the cord at full dilatation of the cervix, a breech extraction was done and Piper forceps applied to the aftercoming head. The vertex was delivered in the occiput anterior position. The infant showed signs of asphyxia, but responded favorably to resuscitation efforts. There was a tendency for the head to return to its fetal attitude after delivery. A cephalhematoma and some flaccidity of the lower extremities were noted. Early improvement occurred, but one month later it was apparent there was a transection of the cord at the level of T-1. Upon looking at the hyperextended attitude of the breech in utero it is possible that the lesion in the cord occurred as a result of pressure in utero.

In Fig. 3 another case is demonstrated with a marked degree of hyperextension. The present film was taken in the last week of pregnancy prior to the onset of labor. Again, the sharp angulation of the cervical portion of the

spine is to be noted. The face is looking upward; the thoracic portion of the spine is also hyperextended. The arms are in front of the fetus with the forearms hanging downward. After eleven hours of early labor, the patient came to the Clinic and examination revealed the cervix to be 4 cm. dilated. There was a single footling breech presentation. The fetal attitude was rechecked by x-ray and no change had taken place. Because the patient had a contracted pelvis (anthropoid configuration with a narrow transverse diameter of the inlet), a low-flap cesarean section was done. An apparently normal infant weighing 2,940 Gm. was born. Incidentally, a nuchal hitch was encountered when extracting the fetus through the uterine incision. The poor flexion of the arms undoubtedly predisposes to the occurrence of nuchal hitches.

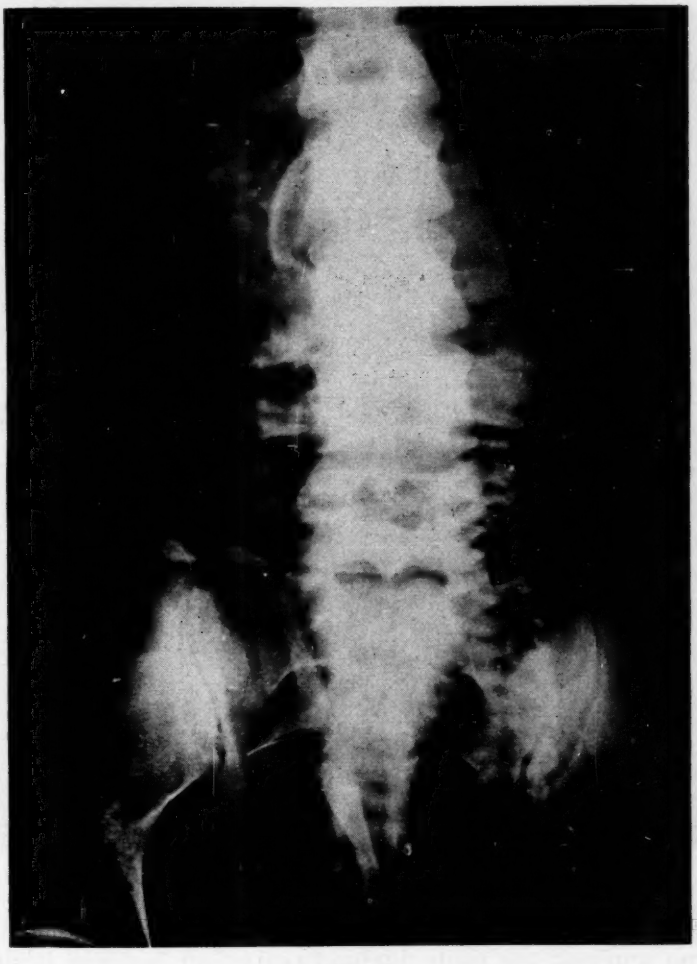

Fig. 1.

These last two cases represent our most extreme cases of deflexed attitudes, and the management of such cases would seem to demand especial attention. Vaginal and abdominal deliveries were accomplished in the two cases, respectively. Because the result with vaginal delivery was unfortunate in the first case, we do not feel that all such cases should have a cesarean section per se. Individualization of each patient with such a problem would seem to be the best

approach. In Table VII the results in twenty-three cases of hyperextension of the vertex are summarized. Not all of these cases were deflexed as much as the two demonstrated cases. They all, however, were extended beyond the neutral or military attitude. In the data presented in this brief summary, it is seen that four patients were delivered by cesarean section. Two of these had contracted pelves, and in one the diagnosis of placenta previa was made. The fourth

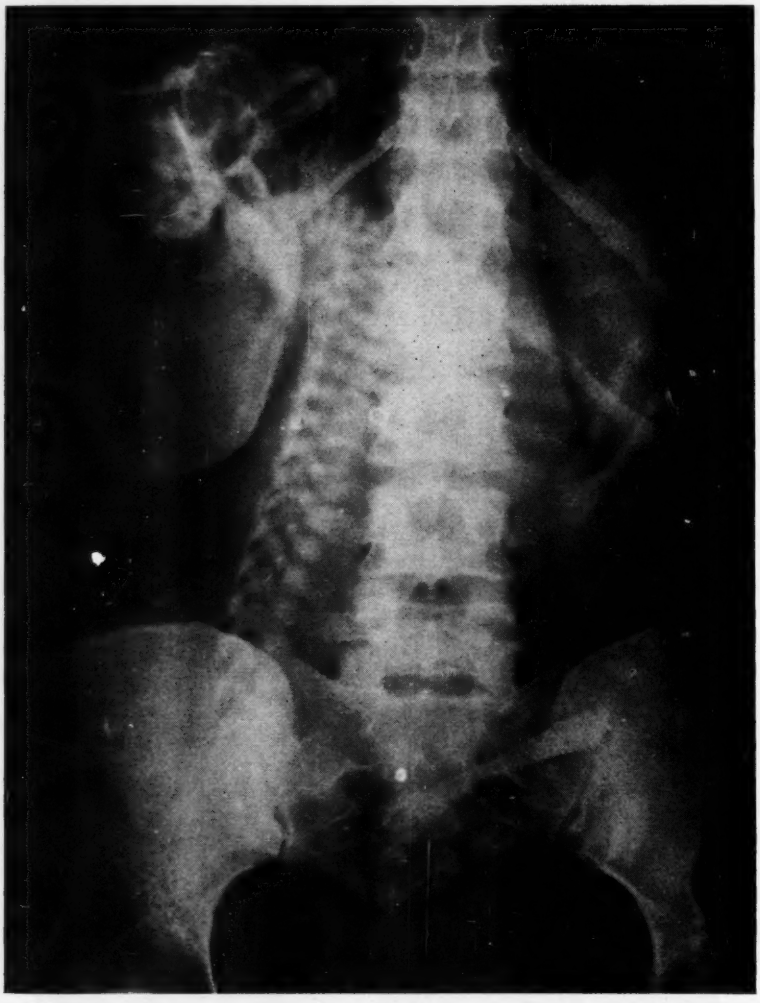

Fig. 2.

had an abdominal delivery; no other feature complicated the clinical course except that no progress was made during twenty-four hours of labor. Incidentally, a repeat x-ray taken at the end of the twenty-four hours of labor showed no change in the fetal attitude. The incidence of cesarean section in this very small group of twenty-three cases is 17.4 per cent, considerably higher than that of cesarean section in all breech deliveries in this Clinic, which was previously quoted as 4.7 per cent.

Three of the cases with hyperextension had the frank breech decomposed or "broken up." We might add that we do not do such procedures in the Woman's Clinic unless the progress of the breech is arrested.

One infant was lost in the process of delivery. Therefore, the fetal mortality is 4.3 per cent in cases with hyperextension of the vertex. In the instance cited, there was a prolonged labor and a resistant cervix. This death might have been prevented by the employment of a cesarean section at the proper time. In only one instance was there found a congenital anomaly (cyst) of the neck that might explain the hyperextension of the vertex.

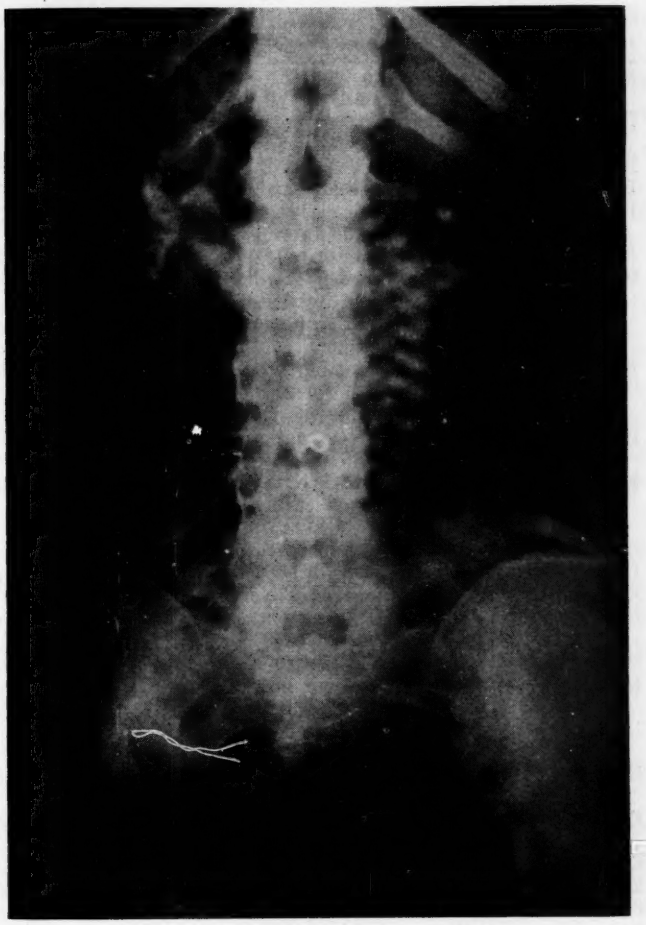

Fig. 3.

The median duration of labor in this group with hyperextension of the vertex is eighteen hours. However, the four who had abdominal deliveries were excluded from these figures. The two patients who had labor prior to their sections obviously were destined to have a period of labor considerably longer than eighteen hours.

It is our opinion that the series of cases with hyperextended heads is too small to be statistically sound. However, more operative interference was done in the group of cases with the hyperextended attitude. The duration of labor is no longer for vaginal deliveries (shown in Table VII) than is that of the average primipara in all deliveries.

The x-ray should be utilized when possible in the study of such cases. A flat plate of the abdomen and a lateral may be necessary to evaluate properly the deflexion and in many cases the rotation of the head. The maternal pelvis

should be visualized also to learn the configuration and the measurements. By such adjuncts, more information may be obtained about the mechanism of labor for the breech, the shoulders, and the aftercoming head.

TABLE VII. CLINICAL RESULTS OF BREECH DELIVERIES WITH HYPEREXTENSION OF VERTEX IN UTERO

CASE	HOURS OF LABOR	SPINE, ATTITUDE	TYPE OF DELIVERY	PARITY OF MOTHER	CONDITION OF INFANT
1	None	Extended	Low flap cesarean section (placenta previa)	P	Good
2	None	Extended	Classical cesarean section (contracted pelvis)	P	Good
3	5	Extended	Frank breech extraction	M	Good (4,600 Gm.)
4	5	Hyperextended	Frank breech extraction	P	Good
5	5	Hyperextended	Forceps on aftercoming head and frank breech extraction	P	Good
6	8	Extended	Frank breech extraction	P	Good
7	9	Extended	Frank breech extraction	P	Good
8	13	Hyperextended	Single footling breech extraction and forceps on aftercoming head	P	Good
9	14	Hyperextended	Double footling breech extraction and forceps on aftercoming head	P	Good, but congenital anomaly of neck
10	15	Hyperextended	Low-flap cesarean section (contracted pelvis)	P	Good
11	16	Flexed	Frank breech extraction and forceps on aftercoming head	P	Good
12	16	Hyperextended	Spontaneous breech delivery	P	Good
13	18	Hyperextended	Spontaneous breech delivery	M	Good
14	20	Hyperextended	Frank breech delivery	P	Good
15	23	Hyperextended	Double footling breech extraction	P	Good
16	24	Hyperextended	Low-flap cesarean section	P	Good
17	25	Hyperextended	Single footling breech extraction and forceps on aftercoming head (prolapsed cord)	P	Asphasia Paralysis
18	25	Extended	Decomposition; frank breech extraction	P	Good
19	26	Extended	Decomposition; frank breech extraction	P	Good
20	28	Extended	Frank breech extraction	P	Good
21	49	Extended	Frank breech extraction	P	Good
22	64	Extended	Frank breech extraction	P	Good
23	67	Extended	Decomposition; frank breech extraction	P	Deadborn

Median Duration of Labor:	Hyperextended head (excluding Nos. 1, 2, 10, 16)	18 hours
	Total breech deliveries	11 hours
	Vertex presentations	10 hours

Summary and Conclusions

At the Woman's Clinic of the New York Hospital, a study has been made of the full-term and premature deliveries in breech presentation. Emphasis has been placed on the attitude of the fetus as shown by radiological studies. Brakemann drew attention to the problem of the deflexed head in 1936.

The data of our breech deliveries have been tabulated. One thousand nine hundred eighteen breech deliveries occurred in 45,837 full-term and premature

deliveries. The incidence of breech presentation is 4.2 per cent. The fetal mortality rate in breech deliveries is 14.8 per cent for multiparas and 9.8 per cent for primiparas, a total gross fetal mortality rate of 12 per cent. The corrected fetal mortality rate is 6 per cent if premature infants and congenital anomalies are eliminated.

Prematurity, congenital anomalies, intrauterine asphxia, prolapsed cord or cord tight about the neck, intrauterine infection, intracranial hemorrhage, and premature separation of the placenta are the major causes of fetal death in our breech deliveries. The only significant difference noted in the fetal deaths of multiparas and primiparas was that prolapse of the cord and cord tight about the neck occurred in multiparous patients more than twice as often as in primiparous patients.

Cesarean section carries with it a lower fetal mortality rate in breech deliveries, 4.4 per cent, which is about one-half that of other types of operative deliveries.

Maternal mortality in breech deliveries is 0.31 per cent.

The neutral or military attitude of the vertex is most commonly encountered in breech presentation. The duration of labor with the vertex in the neutral attitude is shorter than in those with the vertex flexed or hyperextended.

The theory that extreme hyperextension of the vertex may be responsible for longer labor is not proved by this small series of cases. The incidence of cesarean section was more than four times as high in the cases with extreme hyperextension of the vertex as in all deliveries of the Clinic. The fetal mortality in the summarized cases of extreme hyperextension is 4.3 per cent. We do not believe cesarean section is indicated because of a hyperextended vertex per se. Individualization of such cases must be stressed. The study of the mechanism of labor in each case by means of the x-ray will aid in the management of the hyperextended breech presentation.

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TUBAL STERILIZATION THROUGH THE VAGINA*

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IT IS not the purpose of this paper to discuss the moral or ethical problem of sterilization. This is a question which must be decided by the patient, her husband, and the consulting physician. Certainly, the religious beliefs of both the patient and physician should be respected; however, it is our opinion that a married couple has the right to determine the size of their family whether this be accomplished by total abstinence, contraceptives, or sterilization.

In a review of the literature and present-day textbooks, one is impressed by the variety of techniques still advocated for sterilization notwithstanding that there have been fewer failures reported following the Pomeroy technique. Pregnancies continue to be reported after the performance of preventive operations regardless of the technique that has been used. Many additional reports in the literature indicate that pregnancy can occur even after removal of a major portion of the uterus. This further substantiates the statement that hysterectomy with bilateral salpingo-oophorectomy is the only positive safeguard. Until the perfect operation is devised, we are confronted, therefore, with the problem of choosing the safest, most appropriate, and most effective method of sterilization in that large group of women in whom such a mutilating operation should not be considered.

In an extensive résumé of the literature Knight,[1] in 1946, compared the results obtained with the Pomeroy, the Madlener, and resection of the cornu methods of sterilization. He concluded that the Pomeroy is the safest, simplest, and the most easily performed method, that it produces 50 per cent better results than the Madlener technique, and that the cornual resection technique is least efficient. The reports of Lull[2] and Thornton[3] in 1,031 patients with no failures substantiate these conclusions. It should be pointed out that a majority of the sterilizations reported in the literature were done on the pregnant or puerperal uterus. We should like to suggest that the conditions and changes resulting from pregnancy may be a factor in many of the failures and that failure is not entirely due to the technique used. However, Lull's results in 812 cases suggest that this conclusion may not be valid. Four of the five deaths reported in this series, however, followed operations on the pregnant or puerperal uterus and we believe that this lends weight to the conclusions which we shall discuss later in this paper.

It has long been our feeling that sterilization at the time of therapeutic abortion is an unsatisfactory and at times dangerous procedure. I have witnessed the death of a young married woman upon whom a therapeutic abortion and sterilization had been performed for rheumatic heart disease. She developed a pelvic cellulitis and her damaged heart could not resist the added load of the infection.

*Presented before a meeting of the Chicago Gynecological Society, May 21, 1948.

This report includes sterilizations done at the time of therapeutic abortion but not those performed at the time of cesarean section. Undoubtedly, the number would be much larger were it not for the fact that we have performed vaginal hysterectomy as the means of sterilization in many cases, particularly in older women because of co-existing pelvic pathology, such as prolapsus uteri, badly lacerated cervices, small fibroids, uncontrollable menorrhagia, or severe dysmenorrhea. Early in this series most of the sterilizations were accomplished by the cornual resection of the tubes but more recently most of us have used the original Pomeroy technique or a slight modification of it, exclusively. We routinely label the resected portions of the tubes, left and right, and send them to the pathologic laboratory for histologic verification that we have resected a portion of the tube in its entirety. This procedure is particularly important if one insists on doing a sterilization in conjunction with therapeutic abortion, as the tubes are more difficult to identify in the presence of an enlarged uterus and their recognition may not be easy because of the associated hyperemia and edema. Some of the failures reported following attempted sterilizations might have been due to the resection of a portion of the round ligaments instead of the tubes. It is important that the entire tube be visualized and traced out to its fimbriated end. This is especially so when the operation is performed per vaginam or through a small abdominal incision immediately following delivery. The raw stumps must be carefully inspected for bleeding before dropping them back in the pelvis.

As far as we are able to determine we have had only one failure with either Pomeroy or cornual resection technique when performed on the nonpregnant uterus. Perhaps others have had the opportunity of seeing some of our failures. As we shall point out later, sterilization done at the time of therapeutic abortion has not been as successful when the cornual resection technique has been employed. In recent years we have abandoned the routine testing of the patency of the tubes ten to twelve weeks following the operation, feeling that patency might be re-established by this procedure. It is well known that tubal epithelium possesses unusual ability to regenerate after injury, whether it be traumatic or inflammatory in origin.

Dippel,[4] in 1940, in a critical analysis of five failures of the Madlener technique was able, at subsequent laparotomy, to demonstrate by serial sections of the operation sites that failures were due to tuboperitoneal fistula or canalization of the damaged lumina. One can easily visualize how the instillation of any opaque medium or air might re-establish tubal patency in some cases.

Dieckmann and Hauser,[5] in a report of failures of tubal sterilization using the Madlener technique, had the highest percentage of failures in their twenty-four-hour post partum cases. They point out that the alterations of the tubes in association with pregnancy may be factors in these failures. With this we concur. We cannot agree with their statement that their failures when using the vaginal technique should be due to difficulty in exposing the tubes unless they were operating on the pregnant uterus.

We believe that laparotomy for sterilization alone is an entirely unjustifiable procedure, except perhaps postpartum sterilization in selected cases, as suggested by Adair and Brown[6] before this Society in 1939. We do not do as many postpartum sterilizations as are done in other hospitals, ours being limited to those patients having very little outlet relaxation and in some patients who have been unable to use contraceptives successfully, thereby presenting an economic and social problem. We believe that most patients who have had several vaginal deliveries, in whom sterilization is indicated, have in addition so much outlet relaxation that vaginal plastic surgery is also generally indicated. In such cases, we prefer that the patients return at a later and safer date for sterilization and plastic repair. It has been our experience that the ideal time for this procedure is approximately four to six months post partum. Involution is by no means complete in six weeks as stated in the standard textbooks on obstetrics. We believe that the operative risk is lessened and the chances of failure of the tubal sterilization are decreased in direct ratio to the stage of involution. Nearly all of the complications encountered have occurred in patients who have been sterilized at the time of therapeutic abortion or on incompletely involuted uteri. These complications have not been critical, but when superimposed upon such conditions as severe heart, kidney, or pulmonary disease they may be a deciding factor in the patient's recovery.

In most of these reports no mention is made of mortality except the five deaths reported by Lull in his series of 589 sterilizations by the Pomeroy technique. Four of these five deaths were in women who were pregnant at the time of sterilization. The other woman died following a vaginal plastic and sterilization and Lull explains that the sterilization had no bearing on the outcome. Of the four pregnant women, one died following cesarean section and sterilization and death resulted from the primary indication for surgery. Three had hysterotomies and sterilization and we assume that these were done by laparotomy. We feel that had these uteri been emptied vaginally and the sterilizations been postponed until involution was complete, the end results would have been more successful. However, if these hysterotomies and sterilizations were performed per vaginam, the additional technical difficulties due to an enlarged vascular uterus, increased operative time, and prolonged anesthesia with the resultant bleeding and trauma, all superimposed upon a poor operative risk, probably may have been sufficient to influence the fatal outcomes.

Due to the impetus given by Dr. N. Sproat Heaney in the field of vaginal surgery, all at Presbyterian Hospital are convinced that when it becomes necessary to empty the pregnant uterus (even up to the period of viability), it is much safer to do so vaginally rather than by the abdominal route. Moreover, we feel just as strongly that sterilization should not be done at the time of vaginal hysterotomy except in rare instances.

This paper covers a series of 169 patients on whom sterilization was done on the nonpregnant uterus. The age distribution is indicated in Table I.

The indications for sterilization are shown in Table II.

TABLE I. NONPREGNANT AGE GROUP

18 to 19 years	4
20 to 29 years	51
30 to 39 years	106
40 and over	8
	169

TABLE II. INDICATIONS FOR STERILIZATION

Pelvic pathology	105
Neurological	24
Cardiac disease	15
Kidney disease	9
Pulmonary tuberculosis	5
Sociological	5
Diabetes	4
Repeated fetal malformations	1
Ulcerative colitis	1
	169

In this series of 169 cases there were associated physical complications as indicated in Table III.

TABLE III. ASSOCIATED PHYSICAL COMPLICATIONS

Rectocele	104
Cystocele	68
Urethrocele	35
Lacerated cervix	13
Prolapse of uterus	5
Vesicovaginal fistula	1
Third degree tear	2

In addition to sterilization other operative procedures were performed on these 169 patients as shown in Table IV.

TABLE IV. ADDITIONAL OPERATIVE PROCEDURES

Dilatation and curettage	169
Perineorrhaphy	104
Anterior repair	68
Urethroplastic	35
Amputation of cervix	15
Vaginal round ligament shortening	14
Miscellaneous	4

The technique of sterilization and the hospital stay are indicated in Table V.

TABLE V. TECHNIQUE OF STERILIZATION

Pomeroy, posterior colpotomy	64	62.7 per cent
Pomeroy, anterior colpotomy	42	
Cornual resection, anterior colpotomy	35	34.9 per cent
Cornual resection, posterior colpotomy	25	
Defundectomy, anterior colpotomy	3	2.4 per cent

HOSPITAL STAY

Pomeroy (without plastic)	6.4 days
Cornual resection (without plastic)	10.2 days
Sterilization and vaginal plastic	11.0 days

There were no deaths in the series. There were 52 cases of sterilization without plastic. There was a morbidity of two days in three cases. There were 117 cases of sterilization and additional procedures, with morbidity in 31 cases, an average of 4.9 days (Table VI).

TABLE VI. Morbidity

Sterilization without plastic	52 cases
Cases of morbidity	3 (2 days)
Sterilization and additional procedures	117 cases
Cases of morbidity	31 (average 4.9 days)

The etiology of the morbidity is indicated in Table VII.

TABLE VII

Pelvic cellulitis	15
Cystitis	8
Bladder injury	1
Pelvic abscess	2
Postoperative bleeding	2
Pneumonia	1

There was only one failure in the vaginal sterilization on the nonpregnant uterus, a percentage of 0.59 per cent. The technique employed was cornual resection (Table VIII).

TABLE VIII

Vaginal sterilization on nonpregnant uterus	169 cases
Failures (cornual resection)	1 or 0.59 per cent

A ten-year survey of vaginal sterilization with therapeutic abortion shows the following results:

TABLE IX

TECHNIQUE		SUCCESSFUL		FAILURES	
		NO.	PER CENT	NO.	PER CENT
Pomeroy	19	18	94.8	1	5.2
Cornual resection	11	7	63.6	4	36.4
Total	30	25	83.4	5	16.6

Six of the thirty patients were morbid for an average of five days. The average hospital stay was ten days with no additional surgical procedures having been done.

Conclusions

We have reported the sterilization of 169 nonpregnant patients with one failure. The morbidity was almost nil when no additional surgical procedures were done. The morbidity and hospital stay were markedly increased with the addition of plastic procedures.

Our results with the combination of therapeutic abortion and sterilization have been much less favorable; one failure in nineteen when the Pomeroy technique was carried out and four failures out of eleven when cornual resection was employed. The hospital stay was increased in spite of the fact that no additional plastic work was done. Although there were no deaths following any of the procedures, two patients were critically ill following therapeutic abortion and sterilization.

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Discussion

DR. JOHN I. BREWER.—When sterilization procedures are under consideration, the consulting physician must consider several things before making recommendations. If the sterilization is desired simply because the family is large enough, and if there are no pelvic lesions in the wife that demand surgery, the physician should advise that the husband's vas should be ligated. This is simple, easy of accomplishment, entails no risk, and is preferable to entering the peritoneal cavity of the woman. If there are indications for pelvic surgery in the woman, sterilization may be carried out as a part of that procedure. The author believes that sterilization of the female is best accomplished by ligation of the oviducts vaginally. In most instances this can be accomplished. There are a few exceptions. Tubal ligation or cornual resection procedures are performed abdominally when there is some existing pathology that requires an abdominal approach. If an abdominal hysterotomy or elective cesarean section is indicated, I do not believe that tubal ligation increases morbidity or mortality. From the author's experience and belief, vaginal hysterotomy for termination of a pregnancy is accompanied by increased morbidity and mortality if vaginal ligation of the tubes is carried out as a part of the same procedure. This is quite possible and his reasoning is sound. We shall limit our procedures accordingly in the future. The figures reveal that sterilization procedures are more satisfactorily performed when the patient is not pregnant. The reasons for the failures are not explained. It is apparently a fact, however, that the results are not as good. This and the difficulties encountered when sterilization procedures accompany vaginal hysterotomies confirm a principle that some of us are teaching. This is that surgical procedures should be avoided during pregnancy if at all possible. When surgery must be done it should be limited to the bare minimum. We are in hearty accord with the author's statement that sterilization in most instances is best accomplished several months after the pregnancy is terminated and that the vaginal route is the one of choice. Performance of the procedure through the posterior cul-de-sac is preferable.

We agree that the abdomen should not be opened through an abdominal incision for the purpose of sterilization alone. Postpartum sterilization is rarely indicated. It is, however, a much better procedure than one which was previously performed, namely, a cesarean the only indication for which was a desire to ligate the tubes.

DR. N. SPROAT HEANEY, Beverly Hills, Calif.—I have been greatly interested in advancing the attack on pelvic conditions by the vaginal approach, including sterilization per vaginam. No one who has mastered the technique of vaginal surgery would any more think of entering the abdomen to perform a therapeutic abortion, pure and simple, than an otolaryngologist would think of draining the antrum of Highmore by an incision through the cheek. Because one is not acquainted with some indicated technique is no excuse for him to substitute some more dangerous operation. Vaginal sterilization has been done for years and it is a less intricate operation. One can almost always get perfectly adequate exposure of the tubes through a colpotomy incision.

When an abdominal therapeutic abortion with a sterilization is proposed, it might be well to stop and consider the indications for the operation. If a patient can stand the hazards of an operation of such potentialities, she may well, under most conditions, be allowed to go to term and normal delivery.

Earlier, if the uterus lay anterior, we would do the tubal operation through an anterior colpotomy, especially if an anterior colporrhaphy were also to be done, while if the uterus were retroverted the work would be carried out through a posterior incision. Dr. Boysen indicated in one table the number of operations performed by each approach. He did not show which route yielded the higher morbidity. When a posterior colpotomy is done and the incision is closed by interrupted sutures, if an abscess forms in the cul-de-sac, the sutures will soon give way and the abscess will drain spontaneously, while, if an anterior colpotomy is used, then puncture of the abscess usually becomes necessary and convalescence is delayed. For this reason I always use the posterior approach, rarely have I had to desert this route and do the work anteriorly. The advantages of the vaginal attack over a laparotomy for sterilization are the same as exist between vaginal and abdominal operations generally and need no especial elucidation. I have never done a plain sterilization by the abdominal route.

Though the wishes of the patient must be taken into consideration when a therapeutic abortion or sterilization is to be performed, the physician must assume the full responsibility for the decision and, after the operation is completed, he must impress the patient with the idea that her desires were in no way responsible for his decision. Instead he should unequivocally state that the operation was absolutely necessary. This will protect the patient from psychic trauma and prevent her from deciding at some future date that she had been too hasty in her decision and that another pregnancy is necessary for her happiness. No woman can be more miserable than a patient who has changed her mind regarding the desirability of pregnancy after she has already been "successfully" operated upon.

OBSERVATIONS ON THE USE OF PROGESTERONE IN THREATENED ABORTION

With Special Reference to Pregnandiol Excretion as a Guide to Therapy*†

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THE rationale for the use of progesterone in the treatment of threatened abortion lies in the observation that this corpus luteum hormone is necessary for the maintenance of early pregnancy in experimental animals.[1, 2, 3] Such treatment has been given with the purpose of substituting for a deficiency in progesterone which has presumably led to the symptoms of cramps and bleeding. However, because no deficiency has been demonstrated in the reported cases, it has been impossible to assess objectively the value of this hormone in the therapy of threatened abortion. The various clinical reports show no unanimity of opinion as to dosage or mode and duration of progesterone administration, although, in general, they conclude that this hormone has a beneficial therapeutic effect.[4-9] Despite the widespread use of progesterone in larger doses, there has been no reported significant decrease in the incidence of unintentional abortion. Since nonendocrine factors play a large role in the etiology of threatened abortion,‡ it would seem advisable to demonstrate progesterone deficiency before this therapy is rationally employed and evaluated.

Recent advances in the knowledge of endocrine factors in reproduction indicate that practical methods are available for determining the secretory activity of the corpus luteum and the placenta.[11-15] In the normal menstrual cycle, the formation of the corpus luteum and elaboration of progesterone follow ovulation. After a period of ten to twelve days, regression occurs and menstruation ensues. On the other hand, when the ovum is fertilized, corpus luteum function persists throughout the first trimester of the normal pregnancy, so that production of progesterone is maintained. As function of the corpus luteum decreases toward the end of the first trimester of pregnancy, the placenta takes over the role of secreting this hormone in increasing amounts until shortly before parturition.[13] Thus, in normal pregnancy, the secretion of progesterone proceeds uninterruptedly.

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‡Hertig and Livingston, in studying a series of 1,000 unintentional abortions, observed that 38 per cent were due to a maternal nonendocrine factor.[10]

It has been demonstrated that pregnandiol, a biologically inert steroid similar to progesterone in chemical structure, appears in the urine coincident with the period of activity of the corpus luteum in the normal menstrual cycle and in pregnancy.[13-14] When progesterone is administered to normal men or women, pregnandiol excretion follows.[16-17] From these considerations, it has been generally accepted that progesterone, in the course of its metabolism, is changed to pregnandiol. The site of inactivation is probably in the liver.[18] Pregnandiol is then excreted in the urine. Since the determination of progesterone is difficult, measurement of pregnandiol excretion in the urine has served as an index of progesterone secretion.[16]

Browne, Henry, and Venning were the first to study the excretion of pregnandiol in the urine in cases of threatened abortion.[19] They observed that the majority of patients with symptoms of threatened abortion excreting less than normal amounts of pregnandiol failed to retain the pregnancy. On the other hand, when pregnandiol excretion values remained normal, the symptoms of threatened abortion subsided and the pregnancy resumed a normal course.

Using a rapid, simple procedure for the measurement of pregnandiol in the urine (as a matter of fact, within four hours of obtaining the specimen) our laboratory has studied the variations of pregnandiol excretion in threatened abortion.[20, 21] These observations confirmed those of Browne, Henry, and Venning and others.[22, 23] Furthermore, since excretion values could be determined at frequent intervals, daily if necessary, it was possible to establish the trend of the pregnandiol levels in the urine within forty-eight to seventy-two hours. The data indicated that when such values in instances of threatened abortion remained normal or rose to normal levels from initially low values, the pregnancy was usually retained. Abortion, with rare exceptions, occurred in those cases in which the pregnandiol excretion was persistently lower than normal or fell to low values from previously normal levels. The consistency of these results led to our using the trend in pregnandiol excretion in the urine as a criterion in predicting the fate of threatened abortion. Reports from this and other laboratories indicate that the accuracy of this interpretation of the trend in pregnandiol excretion levels is close to 90 per cent.[21, 24, 25]

The present report is concerned with an evaluation of progesterone therapy in 335 cases of threatened abortion in which urinary pregnandiol studies were carried out. In addition we will discuss the use of progesterone in a special group of nine patients with threatened abortion whose pregnandiol excretions were low, indicating that the prognosis for maintenance of pregnancy was poor.

Materials and Methods

Urine specimens from a group of women with signs and symptoms of threatened abortion were submitted to this laboratory for pregnandiol estimation by the various members of the staff of Michael Reese Hospital. Wherever possible, daily samples were tested. Determinations were made according to the method previously described, on first morning, 12-hour or 24-hour specimens.[26] An excretion of 5 mg. in 24 hours represents the minimal normal value in early pregnancy. A tentative prognosis was made in the laboratory on the basis of repeated determinations indicating the trend of the excretion level.

Information regarding the onset of symptoms of threatened abortion with relationship to the duration of pregnancy, type of therapy, and clinical course was subsequently obtained in approximately 90 per cent of the cases from the physicians participating in this study.

This report is concerned with the findings only in those women exhibiting signs and symptoms of threatened abortion whose pregnancy was of twelve weeks' duration or less. It has been pointed out in a previous communication that pregnandiol excretion is relatively constant in the first trimester (averaging 10 mg. per 24 hours).[20] Fluctuations in the second trimester of pregnancy are large (from 10 to 70 mg. per 24 hours with a rapid increase as pregnancy advances) and, therefore, the trend in excretion is difficult to determine. All cases with evidence of organic general or pelvic pathology were excluded in order to eliminate so far as possible nonendocrine factors contributing to the symptoms or the abortion.

Results

Table I summarizes the results obtained in the analysis of 335 cases. In 155 (46 per cent) the symptoms subsided and the pregnancy continued undisturbed. One hundred and eighty (54 per cent) aborted within ten days of the last pregnandiol determination. Of this series of 335, normal pregnandiol excretion was found in 191 patients. Only 40 women in this group (21 per cent) aborted. Decreased excretion levels, on the other hand, were obtained in 144 patients. Practically all of these women aborted, only four patients (3 per cent) retaining the pregnancy.

TABLE I. SUMMARY OF RESULTS

PREGNANDIOL EXCRETION	NO. OF CASES	CLINICAL RESULTS			
		ABORTION		RETENTION	
		NO.	PER CENT	NO.	PER CENT
Normal	191	40	21	151	79
Decreased	144	140	97	4	3
Total	335	180		155	

Further analysis (Table II) reveals that 104 of the 191 patients excreting normal amounts of pregnandiol received no progesterone therapy. Seventy-seven per cent (80 women) retained the pregnancy. The remaining 87 patients received progesterone in some form, either oral or parenteral or both. The dosage during symptoms varied from 10 mg. of oral anhydrohydroxyprogesterone per day to 25 mg. of the parenteral preparation daily, and represents the range of amounts employed in current practice.[6-9] Eighty-two per cent of these women (71) retained the pregnancy. The difference in retention of 77 per cent in the untreated group and 82 per cent in the treated group is not statistically significant in this series. It appears, therefore, that the progesterone therapy employed in these quantities had no particular effect on the clinical course of threatened abortion associated with a normal pregnandiol excretion.

Decreased pregnandiol excretion was recorded in 144 women. One hundred and six received no progesterone therapy. Of this latter group 103 (97 per cent) aborted and only three women carried to term. The remaining 38 patients were treated with progesterone. Only one patient retained the pregnancy. It is evident, therefore, that progesterone therapy had no appreciable effect in this group of patients.

TABLE II. ANALYSIS OF CURRENT PROGESTERONE TREATMENT OF THREATENED ABORTION

PREGNANDIOL EXCRETION	TREATMENT	NO. OF CASES	CLINICAL RESULTS			
			RETENTION		ABORTION	
			NO.	PER CENT	NO.	PER CENT
Normal	Without pregesterone	104	80	77	24	23
	With progesterone	87	71	82	16	18
	Total	191	151	79	40	21
Decreased	Without progesterone	106	3	3	103	97
	With progesterone	38	1	3	37	97
	Total	144	4	3	140	97

Comments

These observations raise a serious question as to the value of currently employed dosages of progesterone in threatened abortion, and possibly as to whether it has any value at all. It has been pointed out that the rational for the use of progesterone in threatened abortion is in part based on the demonstration that this hormone is necessary for the maintenance of pregnancy in ovariectomized animals. It would appear, therefore, that the substantiation of a deficiency in the secretion of progesterone should form one of the criteria for the treatment of this clinical state with this hormone. In view of the technical difficulty of the estimation of progesterone itself, urinary pregnandiol determinations have been employed in this study to serve as an index of progesterone secretion.

Of the 335 patients reported in this series, 191 (57 per cent) excreted normal amounts of pregnandiol and thereby demonstrated an adequate normal secretion of progesterone. Since there is no deficiency in these cases, one would not expect progesterone therapy to influence the clinical course. This concept is borne out by the fact that approximately 80 per cent of these patients, whether treated or untreated, did not abort. In view of the apparently normal endocrine relationships in these cases, at least with respect to progesterone, one must look to other reasons for the occurrence of the forty abortions. In this study, we have not examined the specimens for ovular defects. Since general and local organic disturbances were apparently eliminated as etiological agents, we have no adequate explanation at the present time except to state that these abortions were probably nonendocrine in origin.

One hundred and forty-four of the patients (43 per cent) excreted less than normal amounts of pregnandiol. These women demonstrated a deficiency in the secretion of progesterone (i.e., pregnandiol excretion of less than 5 mg. in 24 hours). Consequently we might assume that in these cases, progesterone therapy should favorably influence the course of the pregnancy. However, of the 38 women in this group who were so treated, 37 (97 per cent) aborted. Similarly, 97 per cent of the 106 untreated women lost the pregnancy. The abortion incidence in this group remained at 97 per cent whether or not treatment with progesterone was instituted.

Attempts to explain the failure of current progesterone therapy in these patients have led to the following questions:

(1) Were the amounts of progesterone employed adequate to replace the apparent deficiency in secretion by the patient?

(2) Does the persistence of decreased pregnandiol levels in the urine indicate that therapy is being given for a pregnancy which is no longer alive?

The question of adequacy may be answered by the following considerations. In this discussion, we have utilized pregnandiol excretion as an index

of progesterone elaboration. A deficiency of progesterone secretion in early pregnancy is manifested by decreased pregnandiol excretion. Therefore, an adequate replacement dose would appear to be that amount of progesterone which raises the pregnandiol level to the values observed in normal early pregnancy. The average pregnandiol excretion in normal early pregnancy is 10 mg. per 24 hours.[19, 27] When progesterone is administered to human beings a variable amount is recovered in the urine as pregnandiol according to the clinical state.* Thus, when progesterone is given to a nonpregnant woman in the preovulative phase of the cycle, approximately 10 per cent appears in the urine as pregnandiol. The administration of progesterone to a pregnant woman, for reasons yet unknown, leads to about a 25 per cent conversion. In other words, the normal pregnant woman converts 15 per cent more of the progesterone into pregnandiol. In threatened abortion demonstrating decreased pregnandiol levels, one cannot predict whether the response to the administration of progesterone will result in a 10 or 25 per cent excretion of pregnandiol. In order to be sure, under any circumstances, that a normal excretion of at least 10 mg. of pregnandiol in 24 hours would be obtained in these patients, the daily dose of progesterone employed should approximate 100 mg. Therefore, the amounts of progesterone used in the series analyzed above (from 1 to 25 mg. per day) appear totally inadequate.

In an attempt to clarify first the question of adequacy of progesterone dosage, and second, the significance of persistent decreased pregnandiol excretion in early pregnancy threatened with abortion, the following study was initiated. A group of thirteen patients in the first trimester of pregnancy with symptoms of threatened abortion and two consecutive low pregnandiol values in forty-eight hours was hospitalized. Four patients received daily intramuscular injections of peanut oil. The other nine patients received 80 to 120 mg. of progesterone† in the same volume of peanut oil intramuscularly each day until symptoms subsided or abortion occurred. The four patients receiving peanut oil aborted within four to five days after initiation of therapy. Of the nine patients receiving adequate substitution doses of progesterone, four retained the pregnancy. The percentage of retention (45 per cent), even though the series is still small, seems to be significantly related to the therapy, considering that in the larger series discussed above, only 3 per cent carried to term. Studies on a larger number of cases are in progress to test these suggestive, but inconclusive, results. Details will be reported later.

This small series suggests that the use of adequate doses of progesterone may permit the survival of some pregnancies which, according to our criteria, would otherwise end in abortion. In addition, these observations imply that the excretion of small amounts of pregnandiol over a period of forty-eight hours in the presence of symptoms does not necessarily indicate that the pregnancy cannot be salvaged. Since pregnandiol excretion can be used as an objective guide in demonstrating the status of progesterone production, and since adequate progesterone dosage can be estimated, it appears that the approach to the treatment of threatened abortion might be guided along such avenues.

Summary and Conclusions

1. The present report emphasizes the necessity for objective criteria in evaluating progesterone therapy in threatened abortion and indicates the

*Observations from this laboratory to be published.

†The progesterone used in this study was generously supplied by Roche-Organon Inc., Nutley, N. J., and the Upjohn Co., Kalamazoo, Mich.

rationale and practicability of utilizing pregnandiol excretion levels in the urine as a criterion.

2. An analysis of 335 patients with threatened aborton is reported, correlating the pregnandiol excretion values and progesterone therapy with the clinical course.

a. One hundred ninety-one patients excreted normal amounts of pregnandiol (evidence of normal progesterone secretion). The incidence of retention of pregnancy in the treated (82 per cent) and untreated (77 per cent) cases in this group was essentially the same.

b. One hundred and forty-four patients excreted less than normal amounts of pregnandiol (evidence of diminished progesterone secretion). Ninety-seven per cent of these patients aborted with or without progesterone therapy.

3. The inadequacy of currently employed dosages of progesterone in this clinical state is suggested.

4. A rationale is outlined for estimating the amount of progesterone which will result in the excretion of normal amounts of pregnandiol in early pregnancy.

5. In a small series of cases of threatened abortion, progesterone was given in amounts estimated to substitute for the progesterone deficiency as reflected by diminished pregnandiol excretion. The results suggest that this therapeutic approach may permit the continuation of some pregnancies which would otherwise end in abortion.

The authors wish to thank Dr. Rachmiel Levine for aid and encouragement in this work. They also wish to express their thanks to the members of the Department of Obstetrics and Gynecology of Michael Reese Hospital for their cooperation in this study. Drs. A. K. Koff and R. A. Reis were most helpful in reviewing the manuscript.

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Discussion

DR. ARTHUR K. KOFF.—This is the largest series of cases of threatened abortion studied to date. Consequently, the results have a statistical value. For the first time we have an accurate laboratory test which is of significance so far as the diagnosis, treatment, and prognosis of threatened abortion are concerned. For example, in any given case of threatened abortion, if the pregnandiol levels are normal (10 mg. or more), it is obviously unnecessary to treat such a case with progesterone. As a matter of fact, in such cases it is largely wasted therapy. On the other hand, if the pregnandiol levels are low, 5 mg. or less, we might reason that the pregnancy is not alive or that, if it is alive, there is deficient secretion of progesterone. Again, in a given case if the pregnandiol level is low we can check whether or not the pregnancy is alive by doing an Aschheim-Zondek or Friedman test. If the Friedman test is positive and the pregnandiol remains at a relatively low level, then I am of the opinion that the patient should be treated with large doses of progesterone. The suggestion that Dr. Tulsky makes is that 75 to 100 mg. should be the average dose if we expect the pregnancy to be maintained. On the other hand, if the Aschheim-Zondek test or the Friedman test is negative and the pregnandiol level is low, we can assume the pregnancy is not alive and there is no need to treat the patient. She should be allowed to abort spontaneously or curettage can be done. It is unwise to make predictions so far as treatment with large doses of progesterone is concerned. However, on the basis of the nine cases that Drs. Guterman and Tulsky presented, four of the nine with low pregnandiol levels carried to term. I believe that if a sufficient number of cases are studied, perhaps we will have a different figure of survival and instead of having an abortion incidence of 79 per cent when the pregnandiol level is low, it is very likely that we may have a survival rate of 40 per cent or over.

DR. A. J. MAUZEY.—The subject of pregnandiol excretion remains confusing and perplexing. As we see it, there are two difficulties. First, are we agreed that pregnandiol excretion is a reasonable index of progesterone metabolism? Second, do we have a reliable method for determining the excretion of pregnandiol?

With all due regard to Dr. Guterman for the excellent presentation tonight, there remains some question as to whether the preceding premises have been established. The fact is, we know very little about progesterone metabolism. We know, of course, from past experiments that when progesterone is given during the corpus luteum phase of the menstrual cycle, there is an increase in the amount of pregnandiol excreted. We know, also, that if progesterone is given during pregnancy, increased quantities of pregnandiol may be recovered from the urine. However, if progesterone is given during the first half of the menstrual cycle, the inactive phase, the amount of pregnandiol recovered is little or nothing. We know further that if progesterone is given throughout the menstrual cycle, the total amount of pregnandiol excreted may be actually decreased. Why is it, then, that the excretion of pregnandiol is definitely increased when progesterone is administered during corpus luteum and placental activity but is greatly reduced or absent altogether when the corpus luteum is in an impaired or nonfunctioning condition? Furthermore, pregnandiol is found in the urine of the human male and will be increased following the administration of progesterone, in spite of the absence of a corpus luteum. The substance is also present in the urine of cases of adrenogenital syndromes. These observations should caution us when placing an interpretation on pregnandiol excretion, particularly as it applies to prognosticating pregnant states.

As to the second premise, that of having a reliable method for measuring the amount of pregnandiol excreted, we wish to state that the first popular assay was reported by

Venning in 1937 and various modifications of that technique have been described since. Dr. Guterman's method of assaying pregnandiol is apparently an improvement over that which has been used before. Certainly, in the light of this paper, it has positive value. Just as Venning and Browne carried the ball for pregnandiol in the early days, followed by Hamlin's carefully prepared contributions, we now have Dr. Guterman advancing in an equally splendid manner with hopes of attaching new importance to this interesting subject.

The subject of ovarian metabolism is one of the most fertile fields in obstetrics and gynecology for research, exclusive of cancer, because the woman's sex life is built around the ovary. If we have now a reliable means for measuring the metabolism of the ovary through pregnandiol excretion, Dr. Guterman has made a monumental contribution. However, we cannot lose sight of the fact that the excretion of pregnandiol is influenced by the quantity of progesterone normally present in the body of the woman, the amount present in the corpus luteum, the excretion capacity of the kidneys and the index of steroid conjugation by the liver. These glaring uncertainties remain with us. Until they are explained, we cannot place an accurate evaluation on pregnandiol excretion.

DR. A. S. TULSKY (Closing).—Because pregnandiol appears in the urine coincident with the period of progesterone secretion by the corpus luteum and placenta, and because the administration of progesterone leads to the appearance of pregnandiol in the urine of individuals who normally would not excrete pregnandiol, it apppears reasonable to assume that pregnandiol is an excretion product of progesterone. Although biochemical studies reveal the presence of other urinary metabolic products of progesterone, pregnandiol is the principal excretion product. The evidence available from studies in the laboratory indicates that the method for pregnandiol estimation which we employ is as accurate and sensitive as any other method in current use.

PREGNANCY AND TUBERCULOSIS

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THE increasing frequency with which tuberculosis is encountered during pregnancy makes the management of pregnancy so complicated an important obstetrical as well as phthisiological problem. The average incidence of tuberculosis when history and physical examination alone are used is 0.75 per cent,[1-5] whereas, when fluoroscopy and x-ray are included in the antepartum examination, the incidence of tuberculosis is approximately 2 per cent.[6-8] When one considers that the incidence of heart disease in pregnancy is between 2 and 3 per cent,[9-10] with a maternal mortality of less than 4 per cent,[9-11] but that the mortality of tuberculosis in pregnancy is from 20 to 35 per cent,[12-14] the management of the tuberculous pregnant woman takes on added significance.

In discussing the effects of pregnancy on tuberculosis one must take cognizance of the type and extent of the tuberculous lesions and compare a similar nonpregnant group of women before arriving at a conclusion. The classification of the National Tuberculosis Association into far-advanced, moderately advanced, minimal, and arrested disease is used in this report to denote the extent of the tuberculous process and the qualitative classification of Ornstein, Ulmar, and Dittler[15] is mentioned in discussing the type of the tuberculosis.

Materials and Method

This report includes 116 deliveries in tuberculous patients whom we have personally attended at Sea View Hospital from 1939 through 1945. All of the patients were treated by the phthisiologists for their tuberculosis and received antepartum care by us. The average stay in the hospital before delivery was three months and the average time in the hospital after delivery was four months. The final result in a patient was determined after her discharge from the hospital or after a follow-up at home. In some instances, following delivery, a thoracoplasty was performed and the patient was not discharged for one year or more. In a small number of cases the patients signed out against advice within one month after delivery. There were 64 white, 50 Negro, and 2 Mongolian patients. The results in these patients are shown in Table I.

TABLE I. RESULTS IN PREGNANT PATIENTS WITH PULMONARY TUBERCULOSIS AS RELATED TO EXTENT OF DISEASE

EXTENT	NO. OF CASES	DIED	UNIMPROVED	NO CHANGE	IMPROVED
Far-advanced	43	20	9	0	14
Moderately advanced	35	2	9	0	24
Minimal	21	0	0	3	18
Arrested	15	0	0	15	0
Osseous	2	1	1	0	0
Totals	116	23	19	18	56

Analyzing these figures, we see that 20 of the 23 patients who died had far-advanced tuberculosis. These 20 patients give a mortality of 46.5 per cent for the group of 43 far-advanced patients, whereas the mortality in the moderately advanced group is 5.7 per cent and there is no mortality in the minimal or arrested groups. There were 19 unimproved patients, only one of whom was worse. Many of these patients signed out of the hospital against advice, and since their condition was neither better nor worse, we have listed them as unimproved. Nine of the 43 patients with far-advanced tuberculosis, 21.2 per cent, were unimproved as were 9 of the 35 patients, 25.6 per cent, with moderately advanced tuberculosis.

Under "No Change" are included those patients whose condition before and for a period of three months after delivery was not altered. All the arrested cases are in this category as are three of the 21 minimal cases, making a total of 18 patients or 15.5 per cent of the 116 patients.

The largest number of patients, 56, or 48 per cent of the 116 cases, were improved following delivery. Comprising this category were 14 far-advanced cases, 24 moderately advanced cases, and 18 minimal cases.

The deleterious effect of pregnancy on the ccurse of pulmonary tuberculosis has been emphasized by many writers.[13, 16-21] However, these authors fail to compare the results in the pregnant group with a nonpregnant group of women with similar tuberculous lesions. More recently a majority of writers, both phthisiologists and obstetricians, have stated that pregnancy does not have a harmful effect on tuberculosis.[12, 22-28] One of the most important factors responsible for the better results more recently obtained in the pregnant tuberculous patient is that the tuberculous disease is treated actively during the pregnancy. This treatment, in addition to the usual bed rest and proper diet, includes pneumothorax, the severing of adhesions and the performance of thoracoplasties *during* the pregnancy. This point cannot be emphasized too strongly, for we believe it is poor therapy to wait three to six months for a pregnancy to terminate before treating the associated medical condition with all the means at our disposal.

In the past few years four thoracoplasties have been performed in the fourth to seventh month of gestation, all with excellent results. In no case did an abortion or premature delivery occur. A number of cases of conception and delivery following thoracoplasty have been reported, the great majority showing excellent results.[29-33]

In a nonpregnant group of women treated at Sea View Hospital from 1939 through 1945, there were 4,455 patients, of whom 30.9 per cent died, compared to a mortality of 19.8 per cent in the pregnant group treated during this period. We do not assume from these figures that pregnancy had a beneficial effect on the course of pulmonary tuberculosis, nor do we advocate that pregnancy be contemplated to improve an existing tuberculous process. Several factors may explain the lower mortality in the pregnant group. First, the number of pregnant patients, 116, is small compared to the 4,455 nonpregnant patients, so that several deaths could produce a significant change in the smaller group. Second, becoming aware of their pregnancy, many women sought medical attention, so that the tuberculosis was diagnosed and treated earlier than occurred in the nonpregnant group. Many of the nonpregnant group were not aware of their tuberculosis until it was far-advanced and only then sought medical care. Such patients, whether pregnant or not pregnant, have a high mortality, as note our mortality of 46.5 per cent in the far-advanced pregnant group. Third, the number of our minimal and arrested cases, 36 of 116, or 31 per cent is much greater than the number of minimal and arrested cases for the hospital, as a whole. Since there were no deaths in the pregnant groups with minimal and arrested

tuberculosis, this would tend to decrease the mortality in the pregnant group as compared to the nonpregnant group.

In tuberculosis, as in most chronic conditions, the later the disease is diagnosed and treated, the poorer will be the end results. Table II shows the results in patients known to have tuberculosis before the onset of pregnancy compared with those women in whom tuberculosis was first diagnosed during the pregnancy.

TABLE II. RESULTS IN TUBERCULOSIS DIAGNOSED BEFORE AND DURING PREGNANCY

	BEFORE	DURING
Died	12	11
Unimproved or no change	27	10
Improved	38	18
Totals	77	39

In the 77 patients whose tuberculosis was diagnosed before the onset of pregnancy, 12, or 15.6 per cent, died compared to 28.2 per cent who died in the group diagnosed during pregnancy. Rist[13] reports a mortality of 51.2 per cent in 117 women whose tuberculosis was first diagnosed during or immediately following delivery.

Effect of Parity on Pulmonary Tuberculosis

In our series there were 70 multiparas and 46 primiparas. The effect of parity on pulmonary tuberculosis is shown in Table III.

TABLE III. EFFECT OF PARITY ON PULMONARY TUBERCULOSIS

	MULTIPARAS	PRIMIPARAS
Died	14 or 20.0 per cent	9 or 19.5 per cent
Unimproved or no change	24 or 34.2 per cent	13 or 28.5 per cent
Improved	32 or 45.7 per cent	24 or 52.2 per cent
Totals	70	46

The percentages for multiparas, 20 per cent, and for primiparas, 19.5 per cent, are almost identical. Six per cent more multiparas showed no change in their condition than did primiparas, and about six per cent more primiparas were improved than were multiparas. We feel these small variations have no significance and believe that parity has no influenec on the course of pulmonary tuberculosis.

Effect of Duration of Labor on Pulmonary Tuberculosis

Most men are agreed that a long, hard labor is to be avoided in the woman with pulmonary tuberculosis, not only because the straining during labor may cause a spread of the disease, but also because the exhaustion and increased blood loss may so weaken her resistance as to cause an extension of the pulmonary disease. The duration of labor was recorded in the 63 patients having vaginal deliveries. Although we realize that the time element alone is not the only factor to be considered, and that several hours of severe, exhausting pains may be more harmful than a longer period of mild or moderate pains, only the time factor could be accurately recorded and used as a basis for comparison. Table IV shows the effect of the duration of labor on pulmonary tuberculosis.

Since it was our intent not to subject any patient to a prolonged labor wherever this was possible, most of the patients, 48 of 63, had a labor of less

TABLE IV. EFFECT OF DURATION OF LABOR ON PULMONARY TUBERCULOSIS

	DIED	UNIMPROVED	IMPROVED
Labor less than 8 hours	11	19	18
Labor 8 to 24 hours	2	3	6
Labor over 24 hours	2	1	1
Totals	15	23	25

than eight hours. Ten had a labor of from eight to twenty-four hours and only three had a labor longer than twenty-four hours. The comparatively high mortality in the patients who had a short labor, 23 per cent, is due in part to the fact that many of these patients had a premature delivery because of their septic condition. The mortality in the four patients who had a labor over twenty-four hours was 50 per cent.

Analgesia and Anesthesia

More harm may result from the improper use of analgesia and anesthesia in the pregnant tuberculous woman than from using no anesthesia and analgesia at all. Alexander[34] states that the preoperative use of narcotic doses of such drugs as morphine, scopolamine, Amytal, and Avertin abolishes or greatly diminishes the cough reflex and the function of voluntary expectoration, not only during the operation, but for a number of hours afterward. During this time the stasis of the pulmonary secretions may cause the development of new areas of infection within the lung. Ether, chloroform, and Avertin are more dangerous than gas or local anesthesia from the point of pulmonary complications because of the relatively prolonged postoperative unconsciousness they produce, during which time the patient does not cough or expectorate efficiently.

In this series, analgesia was used in 35 patients. Morphine and scopolamine were avoided and the drugs most commonly used were Nembutal, paraldehyde and codeine and phenobarbital. No conclusions can be made concerning the efficacy of one drug over the other because the number of cases is too small and because other factors such as the type and extent of the pulmonary disease and the duration of labor must be taken into account. Anesthesia at the time of delivery consisted of local pudendal block in the large majority of cases with the occasional use of cyclopropane or nitrous oxide. In avoiding narcotic doses of drugs and general anesthesia, we have perhaps circumvented their ill effects on the tuberculous patient. This aspect of the problem requires careful individualization with a view to making the patient as comfortable as possible during her labor and yet not depressing her respiration to such an extent that she may suffer a spread of the tuberculosis.

Cesarean Section in Pulmonary Tuberculosis

Because of the high mortality, 46.5 per cent, in pregnancy associated with far-advanced pulmonary tuberculosis, and because we could not foretell the duration of labor in primiparas with large or moderate-sized babies, we decided to do elective cesarean sections on primiparas with far-advanced tuberculosis. We noted that the results in our first fifteen cases were better than those in the group who were allowed to deliver spontaneously; therefore, we broadened our indications to include the less severe types of pulmonary tuberculosis. We have performed 53 cesarean sections, the results of which are shown in Table V.

In this group of 53 patients who had cesarean sections, 8 died and the mortality rate was 15 per cent. This compares favorably with the mortality of 23.8 per cent in the 63 patients who had spontaneous deliveries. Since most of our

TABLE V. RESULTS FOLLOWING CESAREAN SECTION IN PULMONARY TUBERCULOSIS

	DIED	UNIMPROVED	IMPROVED
Far-advanced	8	4	12
Moderately advanced	0	3	14
Minimal	0	0	5
Arrested	0	7	0
Totals	8	14	31

deaths, 20 out of 23, or 87 per cent, occurred in the far-advanced group, we compared our results in cesarean sections and spontaneous deliveries in this group. Table VI shows this comparison.

TABLE VI. RESULTS IN FAR-ADVANCED TUBERCULOSIS FOLLOWING CESAREAN SECTION AND SPONTANEOUS DELIVERY

	CESAREAN SECTION	SPONTANEOUS DELIVERY
Died	8	12
Unimproved	4	4
Improved	12	3
Totals	24	19

The mortality in the 24 patients with far-advanced tuberculosis who had cesarean sections was 33.3 per cent, whereas the mortality in the 19 patients who delivered spontaneously was 63.1 per cent. There were 16.6 per cent unimproved following cesarean section compared to 21 per cent unimproved following spontaneous delivery. Twelve of the 24 patients, or 50 per cent, were improved in the group who had cesarean sections compared to 3 of 19, or 15.8 per cent, in the group who delivered spontaneously.

We are not prepared to advocate cesarean section for all cases of pulmonary tuberculosis, but we are convinced that it has a definite place in selected cases. Patients with contracted or borderline pelves, patients with far-advanced tuberculosis, and patients who have had thoracoplasties during or before pregnancy should be carefully evaluated as to the advisability of a cesarean section. All the cesarean sections were performed under local or spinal anesthesia with the use of phenobarbital as preoperative medication.

Condition of Infants

There were 117 infants born to the 116 patients, including one set of twins. The twins were born prematurely and one twin weighing less than three pounds died. Only one other infant died and this was the child of a patient in whom the fetal heartbeat was lost two weeks before delivery. There were 115 infants who were normal with an average birth weight of seven pounds. None of the infants showed any evidence of tuberculosis and no case of tuberculosis of the placenta was encountered in this series, although we had found one case of tuberculosis of the placenta in a previous series.[35] McCord[36] describes a case of direct intrauterine transmission of tuberculosis from mother to baby. In all our cases the infants were removed to the pediatric building immediately after delivery and the mother was not permitted to breast feed the infant.

Discussion

The treatment of the pregnant woman with tuberculosis must be individualized in that one must differentiate the extent of the tuberculous lesion and the obstetrical complications. Among the latter must be considered the presence of any cephalopelvic disproportion which may cause a prolonged labor, the oc-

currence of any of the toxemias of pregnancy, especially severe vomiting in the first trimester, and the history of previous labors. In our series of 116 patients, the parity seemed to have no influence on the end results. Of great importance, however, was the time when the tuberculosis was diagnosed and treated in relation to the pregnancy. When tuberculosis was known to exist before the pregnancy, the mortality was 15 per cent, in contrast to 29.1 per cent when the tuberculosis was first diagnosed during the pregnancy.

When we compare the end results in pregnant and nonpregnant groups with similar extent and type of tuberculosis, we find very little difference. As a matter of fact, the pregnant group had a lower mortality than the nonpregnant group. The best results were obtained when the tuberculosis and the pregnancy were treated concomitantly and adequately. Although no absolute routine can be given, experience has proved that the best results are obtained when we adhere to certain principles. Patients with moderately advanced, minimal, or arrested tuberculosis who have been controlled for a period of at least six months may be permitted to go into labor, provided no obstetrical contraindication exists, and to be delivered by forceps in the second stage. The pregnant woman with far-advanced tuberculosis must be carefully evaluated. In the multipara with a history of a short, easy previous labor, vaginal delivery may be awaited using forceps at complete dilatation. A primipara or a multipara with a history of long, severe labors should have a cesarean section under local or spinal anesthesia. A long period of bed rest, up to three months or more, as dictated by the tuberculous condition, is indicated after delivery for the tuberculous woman. For analgesia we have found Nembutal satisfactory and prefer local anesthesia at the time of vaginal delivery.

In some instances, even though the tuberculous woman comes through her pregnancy and labor without a flare-up, a breakdown in her pulmonary condition occurs at a later date. Any change in her condition due to parturition should become evident within two months after delivery; any change after that period should not be attributed to her pregnancy or labor. In all probability such exacerbations are due to the patient's undertaking too many household duties and neglecting her rest and diet. The sociological and financial aspects are, of course, to be considered and contribute to the deleterious effects incorrectly ascribed by some to the pregnancy.

Conclusions

1. The incidence of tuberculosis complicating pregnancy when fluoroscopy and x-ray are used in the antepartum examination is approximately 2 per cent.

2. The maternal mortality in our series of 116 cases was 19.8 per cent; 87 per cent of the deaths occurred in the far-advanced group.

3. The mortality in the far-advanced group delivered by cesarean section was 33.3 per cent, whereas the mortality in the far-advanced group delivering spontaneously was 63.1 per cent.

4. Parity has no effect on pulmonary tuberculosis.

5. The mortality when tuberculosis is diagnosed during pregnancy is almost twice as great as when it is diagnosed before pregnancy.

6. The important factor in prognosis for the pregnant, as well as for the nonpregnant woman, is the extent and type of the tuberculous lesion and the rapidity with which treatment can be instituted.

7. Prolonged, severe labor is to be avoided in pulmonary tuberculosis.

8. Nembutal for analgesia and local anesthesia has given good results in our cases.

9. Cesarean section has a definite indication in selected cases of tuberculosis.

10. None of the infants born had evidence of prenatal or postnatal tuberculosis. The infant mortality was 1.7 per cent.

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EXPERIENCE WITH EXTRAPERITONEAL CESAREAN SECTION AT THE UNIVERSITY OF IOWA HOSPITALS

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TWO previous reports[1, 2] have summarized the cesarean section experience at the University Hospitals up to and including the year 1942. Since that time the Waters'[3] extraperitoneal operation has been added to the techniques available for abdominal delivery. It is still uncertain whether this operation offers any real advantage in the grossly or potentially infected patient, but our limited data are presented to assist with its final evaluation.

The clinical management of prolonged labor is not yet standardized and several plans are under trial in different clinics.

1. McKelvey[4] feels that physicians should be able by clinical and x-ray pelvimetry to forecast the probable course of parturition prior to its onset, and that trial labor has little place in modern obstetrics. As a result of this philosophy, his incidence of cesarean section is relatively high.

2. Dieckmann,[5] at the Chicago Lying-in Hospital, evaluates these borderline patients at the end of twenty-four hours of labor or after eighteen hours of ruptured membranes. This short trial labor allegedly provides sufficient time to study the course of labor, does not jeopardize the patient, and reduces the incidence of cesarean section. He feels that low segment cesarean section cannot be done with safety after this interval. Patients who have been in labor longer than twenty-four hours and who require intervention are treated by cesarean hysterectomy, Dührssen's incisions with midforceps, or some type of destructive procedure. It is his opinion that extraperitoneal cesarean section has no real place in modern obstetrics, particularly in the grossly infected patient.

3. Other clinics feel that extraperitoneal cesarean section is the procedure of choice if vaginal delivery does not seem feasible in the grossly or potentially infected patient. By waiting beyond Dieckmann's time limit, many patients can be successfully delivered vaginally. The additional time consoles the operator who no longer has to choose between sacrificing the uterus of a primipara or doing a destructive procedure on a live child or on one who has died from an unsuccessful attempt at forceps delivery.

4. Randall,[6] at the Mayo Clinic, is extending the use of the low flap operation to include patients who have been in labor forty-eight hours or longer. He feels that the apparent safety of the extraperitoneal operation is due to use of the new therapeutic agents, such as antibiotics, chemotherapy, and blood.

5. Eastman[7] and others are forcing labor with Pituitrin in selected cases of prolonged labor without disproportion. In such cases the judicious use of this drug has reduced the incidence of cesarean section 50 per cent and of midforceps 60 per cent. The use of Pituitrin admittedly involves some risk, but it is minimal if contraindications such as disproportion and grand multiparity are observed.

Between July 1, 1926, and December 31, 1947, cesarean section was performed 362 times in a series of 20,416 deliveries, an incidence of 1.8 per cent. There were five maternal deaths, a mortality of 1.4 per cent. The last maternal death associated with cesarean section occurred in May, 1940. The last 188 consecutive operations have been performed without a death in the hospital, but in 1944 one patient died at home from a massive pulmonary embolus two days after her return home.

Table I shows the types of cesarean section done between January, 1940, and December, 1947. Despite fluctuations in the number of deliveries from year to year, the number of abdominal deliveries annually has remained fairly constant with the incidence ranging from 1.2 to 4.0 per cent. The ratio of cesarean sections to total deliveries reached its highest peak (1 in 25) during 1947, due to an increase in the number of repeat operations and to the development of a more liberal attitude toward abdominal delivery.

TABLE I. TYPE OF CESAREAN SECTIONS
JANUARY, 1940, THROUGH DECEMBER, 1947

	TOTAL DELIVERIES	TOTAL SECTIONS	PER CENT SECTIONS	TYPE OF CESAREAN SECTION			
				CLASSICAL	LOW CERVICAL	CESAREAN HYSTEREC-TOMY	EXTRA-PERITONEAL
1940	1913	23	1.2	18	3	2	0
1941	1678	21	1.3	12	5	3	1
1942	1287	19	1.5	7	5	4	3
1943	870	25	2.8	10	8	2	5
1944	588	19	3.2	3	12	1	3
1945	592	20	3.4	0	7	1	12
1946	874	25	2.8	1	7	0	17
1947	991	40	4.0	5	20	1	14

During the four years from 1940 through 1943, the classic operation was the procedure of choice. Since 1944, this technique has been employed only on the occasional patient not in labor, who had placenta previa or transverse presentation. The low flap cesarean section is now more generally used. The first extraperitoneal operation in the University Hospitals was performed in 1941. In 1945 and 1946, it was the most commonly employed procedure for abdominal delivery. In repeat operations the extraperitoneal approach was chosen solely for resident staff training. During 1947, the distribution of the various types has been more equitable. Since adoption of the extraperitoneal approach, cesarean hysterectomy has been reserved for patients with ruptured uterus, severe degrees of ablatio placentae, and large myomas necessitating abdominal delivery.

The fifty-six extraperitoneal sections represent one-third of all abdominal deliveries since 1941. Thirty were performed on patients not in labor and twenty-six after parturition had started. The majority (nineteen) of the latter went into labor spontaneously but seven had labor induced with artificial rupture of the membranes.

Table II shows the indications for the extraperitoneal cesarean sections. Twenty-four of the thirty women not in labor had had previous abdominal deliveries; the remainder had placenta previa, transverse presentation, toxemia, or pelvic contraction. Certain of the twenty-six patients in labor presented multiple indications as shown in the table. Clinically, most of these patients had prolonged labors on the basis of uterine inertia. Clinical and x-ray pelvim-

etry were of little value in determining the method of delivery prior to the onset of labor or even early in labor. According to clinical measurements, eighteen of the twenty-six patients in labor had normal pelves, five generally contracted, one simple flat, and two funnel. The majority of these patients were studied by x-ray pelvimetry (triangulation method), but only one revealed significant pelvic contraction.

TABLE II. INDICATION FOR EXTRAPERITONEAL CESAREAN SECTION

ELECTIVE TYPE—30		PATIENTS IN LABOR—26	
Repeat sections	24	Prolonged labor	15
Primary	6	Uterine inertia	10
1 Placenta previa		Disproportion	7
1 Transverse presentation		Failure forceps	2
1 Generally contracted pelvis		Repeat section	2
2 Funnel pelvis		Toxemia	1
1 Toxemia		Transverse presentation	1
		Face	1
		Brow	1
Total	30	Total	40

Twenty-one of the twenty-six patients in labor were primigravidas. At the time of intervention, the fetal positions were occiput transverse 11, occiput posterior 10, face 1, brow 1, occiput anterior 1, breech 1, and transverse (shoulder) 1. The average preoperative period of labor was forty hours, the longest being 96 hours. The average duration of ruptured membranes was thirty hours. The cervix was 3 to 5 cm. dilated in nine instances and more than 5 cm. in fifteen. Complete dilatation was present twice. The presenting part was usually above the spines.

Seventeen of the patients in labor were grossly infected according to the criteria of Cosgrove[8] (prolonged labor, membranes ruptured for forty-eight hours, evidence of infection manifested by intrapartum chills, rapid pulse, and elevation of temperature). Intrapartum fever occurred in eight of the twenty-six. All but one of the women with intrapartum fever had febrile puerperia; one had marked parametritis, and another femoral thrombophlebitis.

Eighteen physicians performed the fifty-six operations; more than half were done by residents; no single physician did more than twelve. It is believed that the average resident, after assisting with several and after doing two or three under supervision, can reasonably perform the operation.

Spinal anesthesia was used in 41 cases, cyclopropane in thirteen, and caudal twice. In certain early cases inhalation anesthesia was utilized, but was soon abandoned since the long operative time made it difficult to resuscitate the baby.

The operative technique was similar to that described by Waters.[3] The operators generally preferred not to open the peritoneal cavity to facilitate the dissection. Failure to drain the space of Retzius was not followed by an increased incidence of wound infections or serious complications.

The midline abdominal incision was used 33 and the transverse 23 times. Wound infection occurred in 30 per cent of the transverse incisions (the patients not in labor), while none of the midline incisions became infected. Faulty hemostasis and heavy panniculus were the principal factors inclining to wound infection in the former.

The average operative time was one hour and thirty-seven minutes, the longest two hours and fifty minutes, the shortest one hour. In Waters'[9] first group the average total operative time was sixty minutes, but later this was reduced to thirty-eight minutes. The operative time of seventy-three minutes reported by Daichman[10] more nearly approximates our own. This type of

operation requires more time from the initial incision until the baby is delivered, than other types. In this series this time averaged forty-eight minutes; the longest was seventy-eight, and the shortest twenty minutes.

The peritoneum was opened twenty-three times, 39 per cent, not including the cases where it was done purposely to permit tubal ligation. The bladder was injured only once, on the first case.

The blood loss was the same as with other types of abdominal deliveries but two recent patients lost more than 600 c.c. of blood. Williamson[11] warns of the danger of hemorrhage and mentions blood loss as the cause of several extraperitoneal cesarean section deaths.

Postpartum oral temperatures were taken every four hours, and any elevation to 100.4° F. excluding the first twenty-four hours was considered "febrile." By such a criterion, the puerperium was febrile in 60 per cent of the patients in labor and in 50 per cent of those having elective operations. The majority of the fevers were of short duration; only five lasted beyond the fifth day. This approximates the cesarean section morbidity of 57.5 per cent reported from this clinic by Wentsler and Stout.[2]

Thirty-two patients had uncomplicated convalescences. Abdominal distention was noted twenty times, nasal suction was required in eight instances. In the majority of these cases the peritoneum had not been opened and there was no evidence of peritonitis. The ileus was probably due to splinting of the abdomen because of abdominal discomfort. Blood transfusions were given to eighteen patients, penicillin to twenty, and the sulfonamides to ten. The average hospital stay was twelve days, the longest being forty-five days.

There were no maternal deaths. The infant mortality was 5.3 per cent, two neonatal deaths and one stillbirth. Two children with convulsions presented signs of intracranial hemorrhage but survived and seemed normal at discharge. Two women were critically ill as follows:

CASE 1.—Hospital Number 43-2142, aged 20 years, was a primigravida in labor twenty hours, with membranes ruptured eight hours, no vaginal examination, afebrile. Abdominal delivery was indicated by cephalopelvic disproportion. The operative time was sixty minutes, there was no injury to the bladder or peritoneum, the blood loss was less than 300 c.c. Postoperatively, there was a severe puerperal infection with signs of peritonitis. The patient was irrational and critically ill for six days. Several intrauterine cultures revealed beta hemolytic streptococci in pure culture.

CASE 2.—Hospital Number 45-787, aged 25 years, a primigravida, had a trial labor of nine hours with intact membranes, one sterile vaginal examination, no fever. Operative time was two hours and thirty minutes under inhalation anesthesia, the child was severely asphyxiated and had intracranial hemorrhage, but survived. The mother developed either pulmonary embolism or atelectasis soon after operation, and on the following day presented signs of severe infection (not pulmonary). She was acutely ill for several days.

The abdominal delivery of a stillborn child is usually a clinical error. Our patient had been in labor eighty-seven hours before operation, the fetal heart was allegedly heard on one occasion. A flat film of the abdomen, read later, revealed evidence of fetal death. The child showed maceration.

One neonatal death occurred fifteen hours after birth by elective cesarean section; postmortem examination showed pulmonary atelectasis. The other neonatal death represented a real tragedy. The mother had lost two previous children, one an unexplained antenatal death, and the second because of vasa previa with hemorrhage. After a short trial labor, she was delivered abdominally because of lack of cervical dilation and failure of descent of the head. The child weighed 3,900 grams and did well until the tenth day when he was found dead in the bassinet. Postmortem examination revealed congenital cardiac disease, but asphyxia from aspirated food was suggested as the immediate cause of exitus.

TABLE III. SUMMARY OF RECENT EXTRAPERITONEAL CESAREAN REPORTS

NAME	TYPE		TOTAL	MATERNAL DEATHS	FETAL DEATHS	BLADDER INJURIES	PERITONEAL INJURIES	COMPLICATIONS	DRAINAGE	INFECTED CASES
	WATERS	LATZKO								
Aldrich[12]	0	40	40	1*	No note	No note	No note	No note	No note	No note
Cosgrove	323	0	323	3*	No note	4	68	No note	Yes	90
Daichman[10]	100	0	100	0	2	17	36	10 Wound infect. 1 Phlebitis	Yes	76
Eisaman[13]	22	0	22	0	0	1	3	1 Wound infect. 1 Phlebitis	Yes	12
Hanley[14]	40	0	40	0	1	1	20	2 Wound infect. 2 Phlebitis	No note	No note
Irving[15]	59	40	99	3*	No note	No note	No note	No note	No note	No note
Irwin[16]	0	32	32	0	No note	4	5	5 Wound infect.	Yes	18
Keettel	56	0	56	0	3	1	23	9 Wound infect. 1 Phlebitis	No	17
Norton[17]	0	160	160	3*	9	9	44	No note	No note	160
Pieri[18]	65	0	65	0	0	3	7	No note	No note	6 Out of 20 cases
Ricci[19]	175	0	175	1*	7	6	No note	3 Phlebitis	No	No note
Stearns[20]	16	0	16	0	2	3	7	No note	No note	13
Williamson[11]	0	25	25	0	2	0	8	3 Wound infect. 3 Phlebitis	No note	8
Total	855	297	1152	11*	25	49	220	30 Wound infect. 11 Phlebitis		399

*Five due to sepsis.

Discussion

Table III summarizes various recent reports on extraperitoneal cesarean sections. Among 1,152 operations, there were eleven maternal deaths, a mortality rate of 1.0 per cent. Only five deaths were attributed to infection. The supravesical approach was used in 855 patients with six deaths, 0.7 per cent, the paravesical (Latzko) in 297 with five deaths, 1.6 per cent.

Unfortunately, some reports do not give the number of patients with preoperative evidence of infection. However, in 753 cases where such data are available, 399, 54.3 per cent, were grossly infected according to Cosgrove's[8] criteria. There were six deaths in the entire group, a mortality of 0.8 per cent, but it is not clear whether all the fatalities occurred in the infected cases. Even if this is assumed, the death rate still would be only 1.5 per cent.

There were 25 infant deaths, 3.8 per cent, among 658 operations. Considering that many of these women had prolonged labors and in some cases had had attempts at delivery from below, the infant death rate is low.

The bladder was entered 49 times, 4.9 per cent, while the peritoneum was injured 220 times, 26.0 per cent. Wound infection and phlebitis were the most common postoperative complications.

Our experience with the extraperitoneal operation compares favorably with that of others except that the infant mortality is too high, considering that the operation was frequently done for fetal indications. The extraperitoneal approach allows a longer time for evaluation of the patient's ability to deliver herself, but, as with other types of abdominal delivery, too great delay may jeopardize both mother and child. Usually long labors are permitted only in patients with uterine inertia without disproportion.

Many questions concerning the extraperitoneal cesarean section remain to be answered, but our results with the operation in grossly and potentially infected patients requiring abdominal delivery appear to justify continued use of the technique. From 1935 to 1940, there occurred two maternal deaths associated with cesarean section; both women had prolonged labors, were grossly infected at the time of intervention, and were delivered by cesarean hysterectomy. Both received blood transfusions and one was given sulfonamides; both died of peritonitis. Since 1940, seventeen similar cases have been treated by extraperitoneal operation instead of cesarean hysterectomy without a death.

Summary

1. A review of fifty-six extraperitoneal cesarean sections is presented.

2. There were no maternal deaths. Three children did not survive, an infant mortality of 5.3 per cent.

3. Our results with the supravesical extraperitoneal cesarean section have been sufficiently satisfactory to justify our continued use of the procedure in grossly and potentially infected patients requiring abdominal delivery.

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Addendum

During 1948, there were twenty-nine abdominal deliveries; seven were extraperitoneal sections. Four of these patients were grossly infected but there were no infant or maternal deaths.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

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PRIMARY carcinoma of the Fallopian tube is considered a rare entity. This is relatively true, but its occurrence is probably more common than was previously held. In 1888, Orthmann described the first case; since that time, 450 cases have appeared in the literature, with an increasing number in North American publications during the past two decades.

The diagnosis has been mainly dependent upon the observations of the pathologist, for, clinically, primary tubal cancer is extremely difficult to recognize. It is most frequently confused with ovarian tumors, fibromyomas of the uterus, and pelvic inflammatory disease, in that order of frequency.

Pathologically, the gross and microscopic appearance of adenocarcinoma of the tube may so closely simulate papillary adenocarcinoma of the ovary that the latter diagnosis is probably often erroneously made simply because of its known higher frequency. If, however, primary carcinoma of the tube were to be considered in every malignancy of the adnexa, and if multiple sections of the tube were to be examined, this lesion would undoubtedly be reported more often.

Sixty-one cases of primary carcinoma of the tube, appearing in the North American literature during the last sixteen years, have been reviewed and analyzed.

The average age of the patients was found to be 49.5 years, with extremes of 18 and 80 years.

The chief complaints were: (1) vaginal discharge, usually bloody (37 cases, or 61 per cent); (2) low abdominal pain (17 cases, or 28 per cent); (3) abdominal enlargement (4 cases, or 7 per cent). The average duration of symptoms was seven months, with extremes of three days and three years.

Most patients (52 cases, or 85 per cent) had a pelvic mass, of varying size and shape, usually nontender and firm. Five cases had no palpable mass, and four cases had "thickened adnexa."

The correct diagnosis was made preoperatively in only two cases.

The gross pathological description was almost invariable. The tubes appeared elongated and dilated, and were usually involved distally in a cystic mass, which contained yellow, cheesy material or brown, serous fluid. The fimbriated end of the tube was usually closed or indiscernible. On gross inspection, at the time of surgery, a diagnosis of hydrosalpinx was often incorrectly made.

The lesion arose most frequently from the distal one-third of the tube. Histologically, the commonest type was a papillary adenocarcinoma. In 15 cases (25 per cent) the lesion occurred bilaterally.

Forty-eight cases had adequate follow-up study. Of these patients, thirty-one expired in an average of eighteen months; in ten, the prognosis was stated as "poor," because of metastases or recurrence. Thus, 41 of 48 cases were in the nonsalvageable category. Only three patients were living and well five years postoperatively.

Case Reports

CASE 1.—A. E., a 47-year-old Negro woman, first entered the hospital June 15, 1946, complaining of pain in the lower abdomen, of seven days' duration, nausea and vomiting for four days, and increasing size of the abdomen for eight months. The last menstrual period had occurred three years previously.

Physical Examination: A nontender cystic mass, arising from the left adnexa, extending to the level of the iliac crest, was found. Diagnosis of ovarian cystoma was made.

Operation: Bilateral salpingo-oophorectomy and subtotal hysterectomy were performed on June 24, 1946.

Pathologic Report, Gross: The left tube consisted of a 15 by 5 cm. cystic mass. The right tube was slightly dilated. *Microscopic*: The left Fallopian tube contained primary papillary adneocarcinoma, Grade II, and metastases to the myometrium and peritoneal fat were noted. The endometrium and ovaries contained no lesions.

Subsequent Course: The patient re-entered the hospital in November, 1946, with ascites and a palpable abdominal mass, her decline was rapid, and she expired in January, 1947. Consent for postmortem examination was denied.

CASE 2.—L. B., a 65-year-old, white woman entered the hospital Sept. 25, 1946, complaining of obstipation, anorexia, and weakness of five days' duration, and of a mass, increasing in size, in the lower abdomen, of eight months' duration. There had been no vaginal discharge or bleeding since the menopause fifteen years previously.

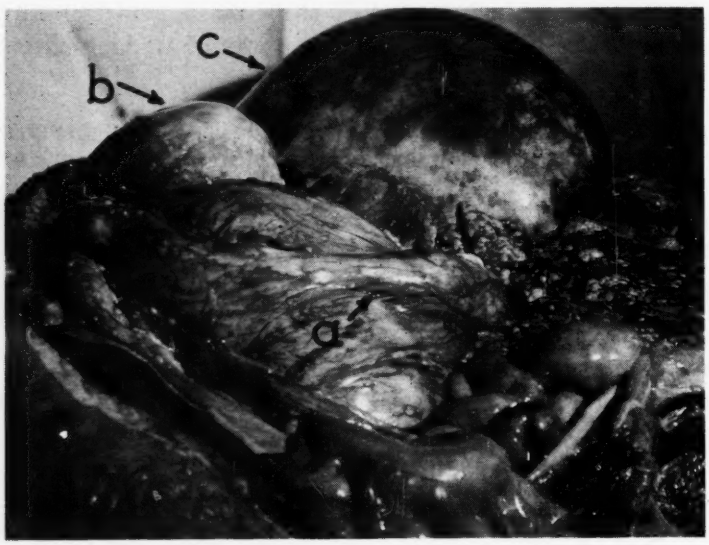

Fig. 1.—Note sausage-shaped left tube (a) running over anterior surface of mass, in which it is involved distally. Mass in center is a calcified, pedunculated fibroid (b). Large cystic mass on right (c) contained black serous fluid. Note peritoneal implants.

Physical Examination: An irregular mass that filled the left lower abdomen, and a separate mass that extended from the right adnexa to above the umbilicus were found. Diagnoses of fibromyomas of the uterus and right ovarian cystoma were made.

Surgery was refused by the patient, her decline was rapid, and she expired Sept. 31, 1946.

Pathological Report, Gross: Both pulmonary arteries were occluded by emboli. The left common iliac vein contained a large thrombus. Both tubes were markedly dilated in the ampullary and infundibular portions. Both became confluent with large cystic masses (Fig. 1). The distal portion of the left tube contained yellow-white caseous material, and

Fig. 2.—Section from proximal one-third right tube of Fig. 1. Shows abrupt change from regular epithelium to papillary type adenocarcinoma. (×80)

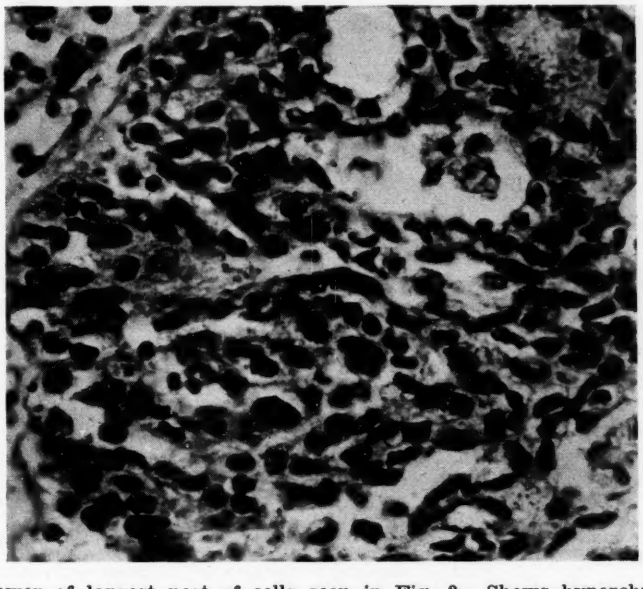

Fig. 3.—High power of largest nest of cells seen in Fig. 2. Shows hyperchromatic nuclei of various sizes and mitotic figures. (×300)

the mass on the right contained black serous fluid. *Microscopic*: Throughout the left tube, there were nests of anaplastic cells with occasional adenoid appearance. The distal two-thirds of the right tube contained a similar lesion, but a section from the proximal one-third showed an abrupt change from regular epithelium to an anaplastic papillary adenocarcinoma

(Fig. 2). Hyperchromatic nuclei of various sizes and mitotic figures were present (Fig. 3). *Diagnosis*: Primary adenocarcinoma of the Fallopian tubes.

CASE 3.—P. W., was a 36-year-old Negro woman, who entered the hospital Dec. 12, 1946, complaining of intermenstrual bleeding of three months' duration, and of a mass, increasing in size, in the lower abdomen, of six months' duration. The last menstrual period had occurred two weeks prior to entry.

Physical Examination: A mass filling the pelvis and lower abdomen was found. A diagnosis of fibromyomas of the uterus with degeneration was made.

Operation: Bilateral salpingo-oophorectomy and subtotal hysterectomy were performed on Dec. 26, 1946. The uterus contained several small fibromyomas, and both tubes were dilated.

Pathologic Report, Gross: The right tube and ovary were incorporated in a cystic mass 10 cm. in diameter. The left tube was dilated to 4 cm. in diameter. *Microscopic:* Both tubes showed masses of adenocarcinoma replacing the mucosa, but the muscle layers were not involved. There was no evidence of malignancy in the endometrium or ovaries.

Subsequent Course: The patient was last seen in November, 1947, at which time a new palpable mass in the left adnexal region was found, which, clinically, was thought to be a recurrence.

CASE 4.—B. L., a 34-year-old Negro woman, entered the hospital July 14, 1947, with complaints of menometrorrhagia and abdominal pain of three months' duration. The last menstrual period had occurred three weeks prior to entry.

Physical Examination: Tenderness throughout the lower abdomen and a mass in the left adnexa were found. The corpus was slightly enlarged. Diagnoses of fibromyomas of the uterus and exacerbation of chronic pelvic inflammatory disease were made.

Fig. 4.—Note clusters of large cells with abundant clear cytoplasm at base of central tubal villus and change in epithelium along edge of large tubal fold on right. (×80)

Operation: Bilateral salpingo-oophorectomy and subtotal hysterectomy were performed on Oct. 15, 1947. The uterus contained small fibromyomas and both tubes were dilated.

Pathologic Report, Gross: The right tube was 11 cm. in length; the fimbriated end was clubbed, but the lumen was present. The left tube was 18 cm. in length, and varied from 5 mm. to 11 mm. in diameter. The infundibular portion formed a cystic mass 10 cm.

in diameter. The lumen was patent proximally, but the ampullary and infundibular portions were occluded by yellow, caseous material. *Microscopic*: The right tube, right ovary, and endometrium showed no evidence of malignancy. The left ovary contained one small area of adenocarcinoma beneath the surface. The proximal portion of the left tube contained clusters of large carcinomatous cells scattered throughout the tubal mucosa (Fig. 4). In

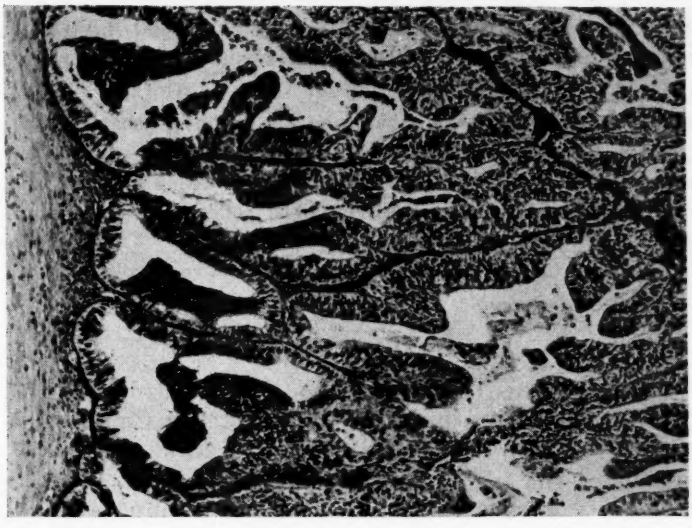

Fig. 5.—Sections taken from more distal portion of tube shown in Fig. 4. Mucosa now entirely replaced by tall folds of high columnar cells which contain various-sized nuclei and mitotic figures. (×300)

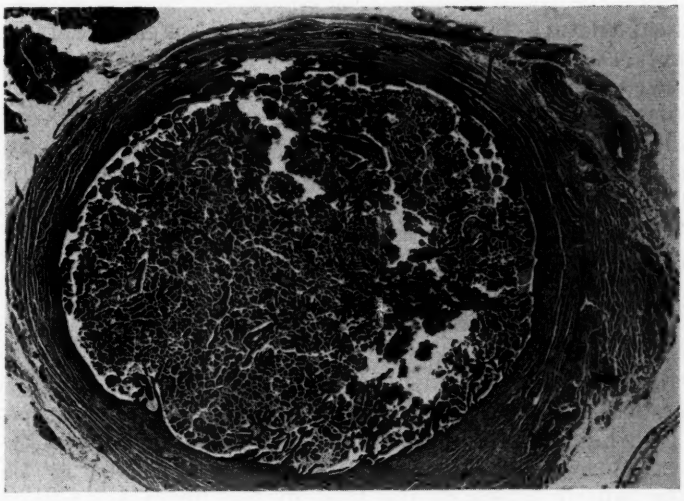

Fig. 6.—Lumen filled with papillary adenocarcinoma that does not invade muscle layer. Folds of tube are flattened, but part of the epithelial surface extends into the solid tumor. Cells have a large pink-staining vacuolated cytoplasm. (×10)

the distal portion of the tube, these cells completely replaced the mucosa and formed tall folds of high columnar cells that contained various sized, hyperchromatic nuclei with many mitotic figures (Fig. 5). *Diagnosis*: Primary adenocarcinoma of the left Fallopian tube.

Subsequent Course: Radiation therapy was begun Nov. 14, 1947, and when seen in February, 1948, the patient was well.

CASE 5.—L. S., was a 44-year-old white woman who entered the hospital Sept. 1, 1947, complaining of a suprapubic mass, a bloody vaginal discharge, and left lower abdominal pain of four months' duration. The menses had been irregular during the previous four years.

Physical Examination: A firm, tender mass filling the lower abdomen was noted. Diagnoses of fibromyomas of the uterus and chronic pelvic inflammatory disease were made.

Operation: Bilateral salpingo-oophorectomy and subtotal hysterectomy were performed on Sept. 10, 1947. The uterus contained small fibromyomas, the right tube was dilated.

Pathological Report, Gross: The right tube was a sausage-shaped structure, measuring 10 cm. in length, and 0.4 cm. to 1.5 cm. in diameter. The distal portion was a multilocular cystic mass, measuring 15 cm. by 10 cm. This was filled with cheesy material and brownish yellow fluid. *Microscopic:* The right tube contained folds of flattened mucosa but part of the epithelial surface extended into the solid tumor (Fig. 6). The left tube, ovaries, and endometrium were not involved. *Diagnosis:* Papillary adenocarcinoma of the distal one-third of the right tube.

Discussion

The five cases presented here were seen during 1946 and 1947. Compared with other reports, this is an unusually high number for so short a period of time. In these years, there were 3,606 gynecological admissions to the hospital.

In the cases here, the average age was 46, with extremes of 34 and 64 years. The chief complaints were abdominal enlargement, unusual vaginal bleeding, and low abdominal pain, in that order of frequency. Two patients presented themselves with symptoms suggestive of mechanical bowel obstruction. All cases had a palpable pelvic mass, and the most common preoperative diagnosis was "fibromyomas of the uterus." Carcinoma of the tube was not considered.

The clinical picture thus simulates many pelvic disorders of the woman near the menopausal age. However, primary carcinoma should be particularly considered when a dilated sausage-shaped tube is observed at the time of surgery. The distal portion is usually involved in a cystic mass. A specimen with this appearance should be opened prior to completion of the surgical procedure, and, if suspiciously malignant, should be immediately examined microscopically. This will preclude a diagnosis of a benign lesion, and will assure adequate surgical treatment.

Most authors of the reports reviewed agree that total hysterectomy and bilateral salpingo-oophorectomy is the operative procedure of choice. Although its efficacy is not established, most of the cases were treated by radiation therapy, postoperatively.

The microscopic appearance of the lesion is that of an adenocarcinoma, usually of Grade II or III. The most common variety is the papillary type. The criteria by which the lesion is determined as primary in the tube are, first, a change from normal to malignant epithelium (seen in Fig. 2); second, no invasion of the muscle layers of the tube by the neoplastic cells (seen in Fig. 6); and, third, no evidence of primary lesion in the ovaries or endometrium.

At times, primary carcinoma of the tube may be indistinguishable from primary papillary carcinoma of the ovary. In these cases it is urged that the pathologic report include at least the possibility of a tubal source. During this study, several such questionable cases were encountered.

The lesion spreads by direct extension and peritoneal implantation. Metastases apparently occur late. The site of predilection could not be determined, but no instance of metastasis to bone was encountered.

Summary and Conclusions

1. Primary carcinoma of the Fallopian tube is a rare lesion, but it is more common than previously believed.

2. Five cases were seen, during 1946 and 1947, in this hospital.

3. Clinically, the diagnosis is extremely difficult to make. However, it should be particularly considered whenever a dilated, elongated tube, involved distally in a cystic mass, is observed at the time of surgery.

4. The microscopic appearance is usually that of a papillary adenocarcinoma.

5. The prognosis is poor.

Addendum

Since the original report, another case was seen and the patient operated upon in March, 1948.

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APPLICATION OF THE VAGINAL SMEAR TO THE DIAGNOSIS OF PREGNANCY

Preliminary Report

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PREGNANCY, from the moment of conception, produces an ovarian state and as such should be recognized in the vaginal smear. It is of utmost importance to establish such a diagnosis during the critical period of an ectopic gestation, not to speak of the many possible gynecological conditions from which it is often necessary that it be differentiated.

Vaginal smears in pregnancy have been described,[1, 2] emphasis being laid upon the specific cells which appear. Most often mentioned are the navicular cells with "enlargement and elongation of their nuclei and thickening of their surface membranes." It is, however, admitted that the recognition requires great experience and is not always dependable because similar cells may be found during the normal cycle.[3]

In the examination of the vaginal smears as they vary in physiological conditions, analysis is far simpler than one is led to believe from the cellular elements involved.[4] This also applies to pregnancy smears as they appear from the time of conception. A direct solution to a problem is desirable; facility of procedure* is attractive, especially if results are immediate. But *no* test should be more than a corroboration of associated findings. From such a viewpoint the following experiences and results are described in the hope that further study may substantiate the stated results.

From the beginning of this study, pregnancy smears, especially those obtained soon after conception and later confirmed, were examined repeatedly. A definite pattern was discernible but no isolated criteria seemed obvious. Further studies on smears before other "tests" were done resulted in correct "guesses" as well as incorrect ones. It soon became evident that negative pregnancies were correctly diagnosed but the positive cases were too often in doubt. On the other hand, these doubtful positives always revealed themselves in findings originally overlooked after pregnancy was confirmed. The difficulty in isolating features common to all remained a stubborn obstacle for a long time. Correct positives which increased in number were attributed to "hunch."

It was soon decided that (1) in the premenopausal delayed or missed period, the widespread differences between ovarian physiological activity and

*Vaginal smears were prepared by obtaining the secretion with a pipette and smearing thinly on a slide. Immediate emersion in alcohol 95 per cent and ether equal parts, for several minutes is necessary in order to preserve the identity of cells. Differential staining can be accomplished within a few minutes by the use of a simple differential stain (by Shorr). The specimens illustrated were stained with an experimental stain, DF 77 A (by Papanicolaou). In general, cornified cells are revealed as red cells, all others are blue.

The writer acknowledges with thanks the assistance given him by Dr. George N. Papanicolaou as well as his generous supply of his single differential stain. He also wishes to thank Schering Corp., Bloomfield, N. J., for supplying Shorr's Differential Stain.

arrested or retarded cyclic changes were obvious; negative pregnancies could be definitely established, the positives were still doubtful; (2) the missed period at any ovarian age might be a freak reaction and followed by the normal follicle ripening of a new cycle; (3) a missed period may be caused by a previously delayed follicle ripening or a prolonged transitional phase (excessive estrogenic elaboration); (4) missed or delayed periods may be part of the general regressive signs of ovarian deficiency as found in hypopituitarism, etc.

These observations were hardly satisfactory in the materialization of the "hunch." One by one, groups of cells or individual forms were selected as possible pathognomonic features of pregnancy. The previously described "pregnancy cells" were not discovered in early cases.

All the physiological factors concerned with pregnancy were reviewed. The life of the corpus luteum begins after ovulation. How it affects the vaginal epithelium during the phase of follicle transition, and after, was the starting point.[4] The functionalis cells are produced in response to corpus luteum stimulation.[1, 4] Unlike the cornified cells found at the estrogenic peak, they are smaller, round or oval, their nuclei larger and characteristically vesicular. The follicle transition phase, not too sharply defined by time or cellular differentiation, may be considered a poised state awaiting hormonal factors to develop. Let us assume that the luteal phase has developed vigorously. Functionalis cells appear in great number while cornified cells diminish rapidly, those remaining showing signs of deterioration. Let us now imagine a single moment of arrested activity, i.e., a moment during which the superficial cells of the vaginal epithelium receive no stimulation from the ovary. Instead of cells being desquamated as a result of proliferation from the deeper layers, they remain in vivo in a static phase, subjected to the effects of stagnant secretions and/or other physical effects. They become frayed, shrunken, their cytoplasm full of debris. By the time they exfoliate, their appearance is altered. The same cell, desquamated during a period of activity, appears fresh and well preserved. This applies to surface cells of any tissue. *This differentiation of cells desquamated while actively influenced by physiological activity and cells shed during periods of retardation or low levels of activity (involution),* I believe to be the most important clue in the detection of pregnancy in the vaginal smears (Figs. 1 and 2).

The peak of function of the menstrual corpus luteum is usually passed by the tenth day after ovulation.[5] As the corpus luteum begins to wane, the functionalis cells, which had been increasing in great numbers and appearing as fresh, vital, well-preserved cells, begin to be irregularly affected. At about the twenty-fourth day, they show signs of deterioration. Twisting, folding, cytoplasm filled with debris, they mass in clumps. The limit of growth and stratification has been reached. Superficial cells bereft of forces which have influenced their activity are now subjected to surface irritation before denudation.

The various premenstrual smears of the normal cycle reveal progressively poorer functionalis cells; debris, leucocytes, and bacteria mount; clumps

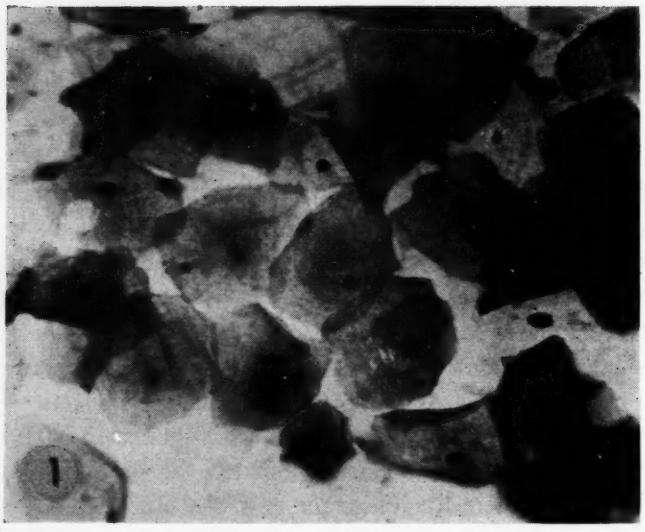

Fig. 1.—Estrogenic peak at end of follicle ripening phase. Uniformity and well-preserved state of cells desquamated during physiological activity.

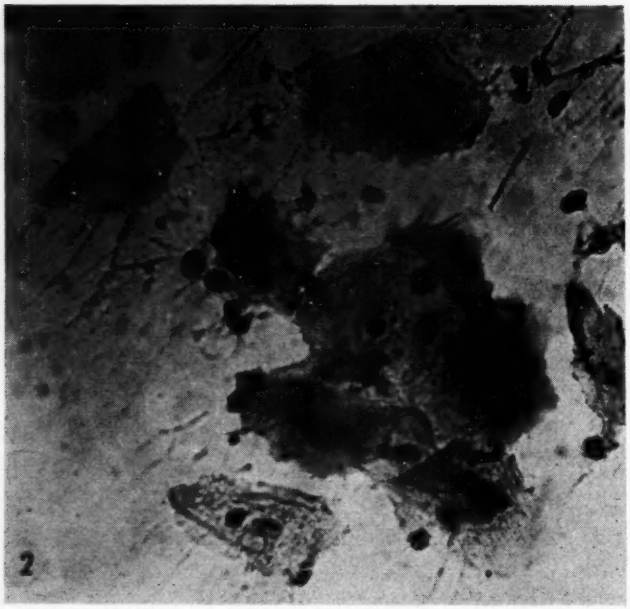

Fig. 2.—Cornified cells after estrogenic peak has passed; no luteinization; show effects of stagnant secretions before exfoliation due to absence of hormonal effects.

become heavier; and deterioration of the cornified cells is complete. Only remnants of their original forms are seen and recognized because of their original "red" stain. The functionalis cells which can be seen outside of the clumps have poor cellular membranes presumed there only because they limit the intracellular contents.

The above observations were obvious findings considered in the study of vaginal smears in general. Their importance in the diagnosis of pregnancy was not recognized at once.

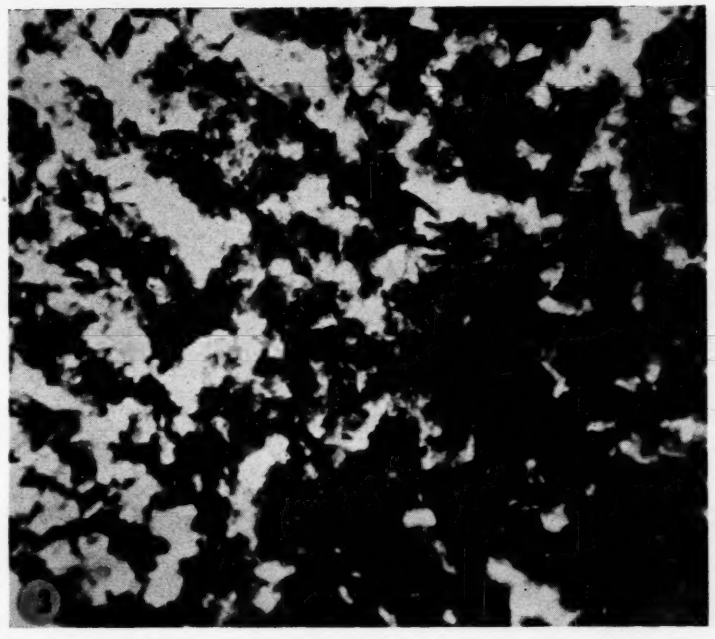

Fig. 3.—Premenstrual smear: note absence of cellular morphology. This black and white print was made from colored transparency which reveals broken, twisted fragments of cornified red cells.

In the event that conception takes place progestational activity continues with no interruption. In fact, a surging influence toward growth and stratification results. The functionalis cells increase in even greater numbers, not a too obvious change; clumping is thinner, also not a very obvious change. The functionalis cells *retain* their freshness, the clarity of their cell membranes and cytoplasm, and the identity of their well-preserved nuclei. These characteristics *are* obvious especially when comparisons are made to smears of the same phase in the normal cycle. The cornified cells, though relatively few in number, too, remain well defined and well preserved, their nuclei perhaps a little larger than those of their predecessors (Figs. 3, 4, and 5).

I found most of the "typical" pregnant smears immediately after conception (Figs. 5 and 6). The rapidly produced functionalis cells are less affected during the early stages when hypersecretion of mucus and excessive debris are less prominent. The differentiating point in doubtful smears depends

Fig. 4.—Well-established phase of luteinization: last menstrual period March 17, 1946: smear taken March 30; note loss of identity of cells near or within clumps. Twisted, deteriorating cornified cells can be detected.

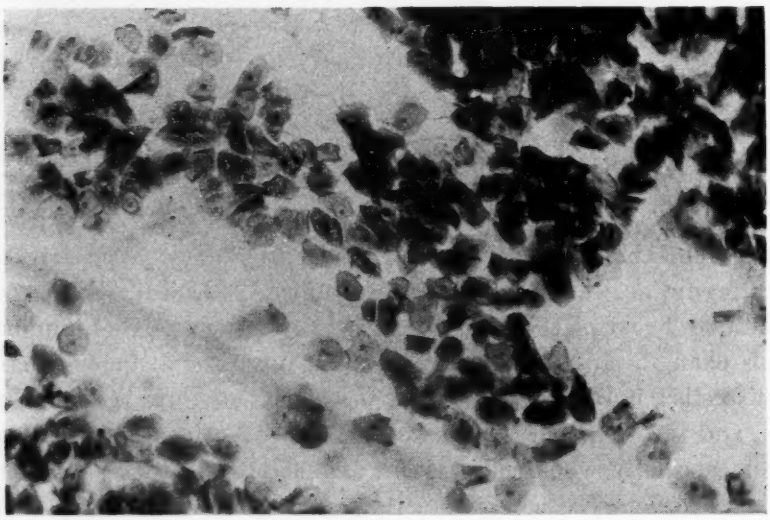

Fig. 5.—Pregnancy smear: same patient as in Fig. 4; smear taken April 4, five days later, nineteenth day of cycle. Note increase in number of functionalis cells, the well-preserved state in and near the clumps, and the absence of other than well-preserved cornified cells. They can be identified by their polygonal shapes. Child born at term, Jan. 11, 1947.

upon a determination as to whether the corpus luteum is involuting or whether it is becoming more dominant. In one case the superficial cells of the vaginal epithelium are left to the physical effects of the surrounding media revealed by the resulting deteriorating effects. In the other case, they are desquamated in

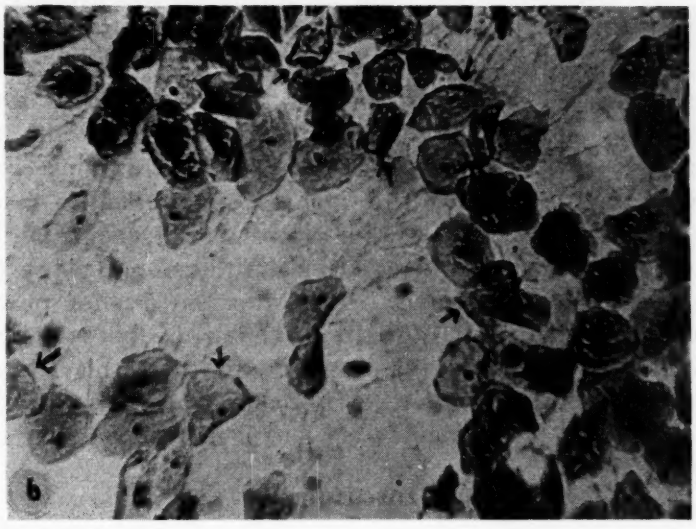

Fig. 6.—Pregnancy smear: ten days after conception; black and white print made from colored transparency. Red cornified cells (arrows) in this field 15 per cent, the others are blue functionalis cells.

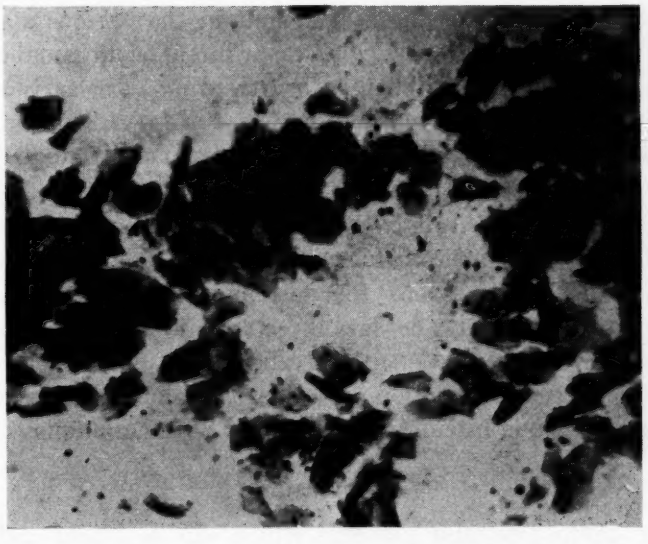

Fig. 7.—Pregnancy smear: six weeks after last menstrual period. Note cells within and about the clumps; they are well defined and have clear cellular membranes (Compare with Fig. 4).

a well-preserved state. The nonpregnant premenstrual smear is thickly clumped, the functionalis cells poorly preserved. The pregnant smears are thinner and fairly well clumped. But in spite of this, by careful focusing, the identity of the cells can be recognized. The cornified cell in the nonpregnant smear is

twisted and folded beyond recognition except for its red color. In the pregnant smear they are in fairly good morphological state (Fig. 7).

No uniformity will be found in a series of pregnancy smears. Cells are not uniformly shed nor are they uniformly affected by the stagnant secretions. The vagina is not regularly swept clean of its contents and with physical factors such as sexual excitation, douching, and infections an otherwise typical picture is altered.

Tracing of vaginal smears throughout the entire period of gestation is not pertinent to the object of this preliminary report of a means of diagnosing early pregnancy. The corpus luteum of pregnancy remains active for one hundred twenty days.[5] The growth of the vaginal epithelium reaches a peak. At that time, it seems that the balance of growth and desquamation leans toward involution. The cells remain in vivo longer and therefore some reveal a "thickening" of their surface membranes. These are the so-called pregnancy cells, cells which are more easily found toward the end of the first trimester and later. No other apparent changes take place except those which may be attributed to physical disturbances. After the seventh month, the smears seem to clear up and appear "cleaner." This may be attributed to a decreased sexual activity.

Discussion

The study of vaginal smears in early pregnancy was premised upon a thorough review of the hormonal influences involved. The conclusions drawn were based upon clinical application of these principles to vaginal smears as they appear in the normal sexual cycle[4] and in the various states of ovarian development.[6] Actual experiences with cases in sufficient number left much to be desired on account of the difficulty in obtaining very early smears. Many specimens were found long after delivery of full-term infants and were discovered by accident while reviewing smears for demonstration purposes.

It has been suggested that smears may be an aid in the diagnosis of pregnancy disturbances. It is reported that a high degree of cornification is a danger signal when associated with hyperemesis, and that deficiency of cornification is associated with severe toxemia and eclampsia.[7] Another report suggests that high therapeutic dosages of estrogenic hormones react very favorably in threatened abortions.[8] In analyzing these hormonal factors, it must be borne in mind that cornification, an estrogenic effect, can hardly be expected in the presence of corpus luteum or deep layers of functionalis cells.

Conclusion

There are definite cellular patterns which can be found and recognized in the vaginal smears immediately after conception. It is firmly believed that they evidence pregnancy and can be detected before the first amenorrheic episode. The interpretation of these findings was based upon the same principles which explain all of the physiological interrelationships which take place in the female sexual tract during its development and in the normal sexual cycle of maturity.

There is still necessity for a great deal of additional observation. Of utmost importance is the question of a persistent corpus luteum. With the accumulation of additional data from many sources, its significance will be given its proper place in these considerations.

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887 Ocean Avenue.

SPECIFIC MALIGNANT CELLS EXFOLIATED FROM PREINVASIVE CANCER OF THE CERVIX UTERI*

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THE diagnosis of cancer of the cervix in its preinvasive phase constitutes one of the greatest challenges to the medical profession. Cure is certain if the abnormal growth is removed before invasion has occurred.[1] While it is impracticable to subject every woman above a certain age to diagnostic surgical procedures, screening for possible cancer can easily be accomplished by the use of the endocervical smear technique. Unless otherwise indicated, diagnostic surgical procedures can be limited to those patients in whom suspicious cells are found in the smear.

Procedure and Results

On routine investigation of 3,700 women of all social strata, twenty-two cases of preinvasive cancer of the cervix and four borderline cases were discovered by means of the endocervical smear technique. The diagnosis was made from biopsies or from endocervical curettage. To obtain material for the smear, an ordinary cotton applicator is inserted about one-half to three-fourths inch into the cervical canal, twirled a few times around and against the squamocolumnar junction. The material is spread evenly on a slide which is then fixed immediately in a solution of equal parts of ether and 95 per cent alcohol and stained by the method of Papanicolaou.[2] Confirmation of a positive smear is always sought by a diagnostic curettage, cervical biopsy, and endocervical curettage.

After detecting the first ten cases of preinvasive cancer, it was noted that the exfoliated cells in smears from preinvasive cancers differ greatly from those of invasive cancer. An attempt has been made actually to distinguish between the exfoliated cells from preinvasive cancer and those from invasive cancers by the difference in cell morphology. In eight of the last twelve cases of preinvasive carcinomas, the diagnosis was suspected from a study of the endocervical smear. All smears from patients with preinvasive carcinoma have been reviewed and in only three out of the total of twenty-two cases was there an absence of the "specific" cells.†

The morphology of exfoliated cells from a preinvasive cancer is extremely diverse and can be distinguished from invasive cancer cells and atypical cells in conditions other than cancer solely by comparison. The main characteristics and distinguishing features of preinvasive cancer cells are the following: They are usually larger than invasive cancer cells and have a greater amount of cytoplasm which usually stains a typical orange-yellow. The nuclei may be either small, hyperchromatic without details, and the nuclear membrane may be very

*Aided by a grant from the American Cancer Society.

†By the screening of a further group of women, twelve patients with preinvasive carcinoma were found. In eleven of these cases the exfoliated cells were those of the preinvasive type, and the diagnosis was made accordingly.

irregular (Fig. 1), or they may be large, foamy and agranular with well- or ill-defined borders (Figs. 3 and 5). On the other hand, nuclei may be found with distinct borders and a particular type of granularity which is never found with invasive cancer (Fig. 7). Bizarre forms, multinucleated or multinucleated giant cells characteristic of invasive cancer, are rarely found in smears when the cancer is in the preinvasive phase. Exfoliated cells from a preinvasive cancer generally

Fig. 1.

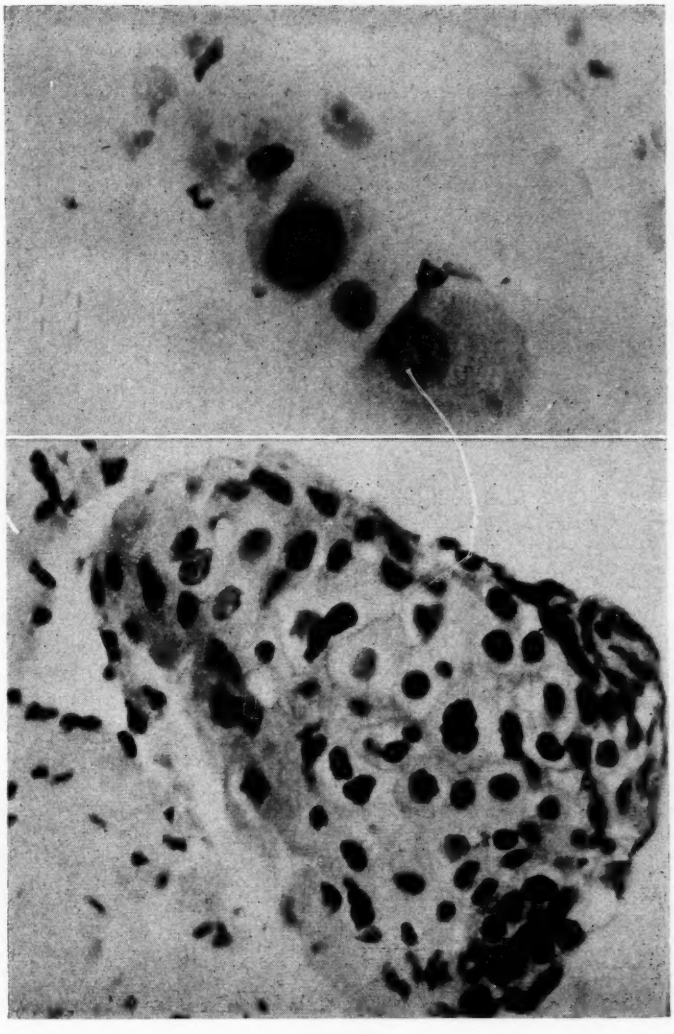

Fig. 2.

Fig. 1.—Endocervical smear. Note small hyperchromatic nucleus with irregular border and two cells with large foamy nuclei. The cytoplasm has an orange-red color.

Fig. 2.—Microscopic section of endocervix; same patient as Fig. 1. In one fragment a minute group of anaplastic squamous cells lying in a cleft.

appear singly or in loose groups but never in adherent clusters. In addition, there is usually a striking predominance of normal cells and the cells in the smears from the vaginal pool may be completely cornified although the patient may be in the luteal phase of the menstrual cycle or of postmenopausal age.

Once the characteristic features of the exfoliated cells are understood, it is relatively easy to distinguish the exfoliated cells of preinvasive cancer from those of invasive cancer. Some difficulty may be encountered, however, in the differentiation of these cells from the atypical cells found in inflammation. When atypical cervical cells are formed and exfoliated as a result of inflammation, they are usually found in large numbers, form adherent clusters and have less cytoplasm than the exfoliated preinvasive cancer cells. Inflammatory cells are more uniform in size and have none of the features described for preinvasive malignant cells.

Fig. 3.

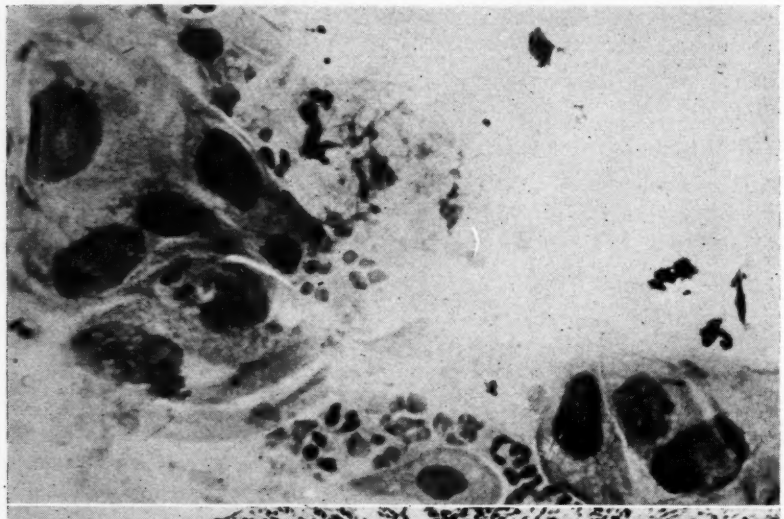

Fig. 4.

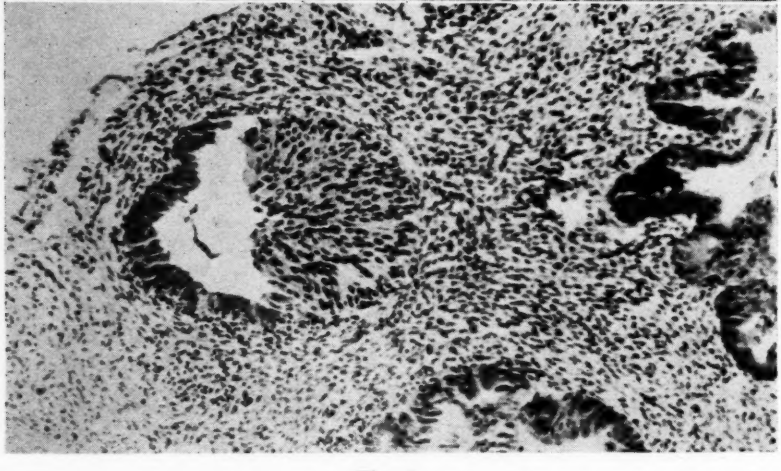

Fig. 3.—Endocervical smear. Note large foamy agranular nuclei with much cytoplasm and two hyperchromatic nuclei.

Fig. 4.—Microscopic section; biopsy of cervix, same patient as Fig. 3. Occasional foci of preinvasive carcinoma in mouths of the glands.

Conclusions

Recognition of the specific characteristics of the exfoliated cells of preinvasive cancer may in the future contribute to the detection of a greater number

of curable cases of cancer. Invasive cancer is usually comparatively easily confirmed by a single biopsy, however, pre-invasive cancer may frequently be missed by one or more biopsies. The knowledge that the case under investigation is probably one of preinvasive cancer may prevent discarding a slide as a false positive in the presence of a first or second negative biopsy. This is important in view of the recent findings of Pund and Auerbach[3] that 3.9 per cent of 1,200

Fig. 5.

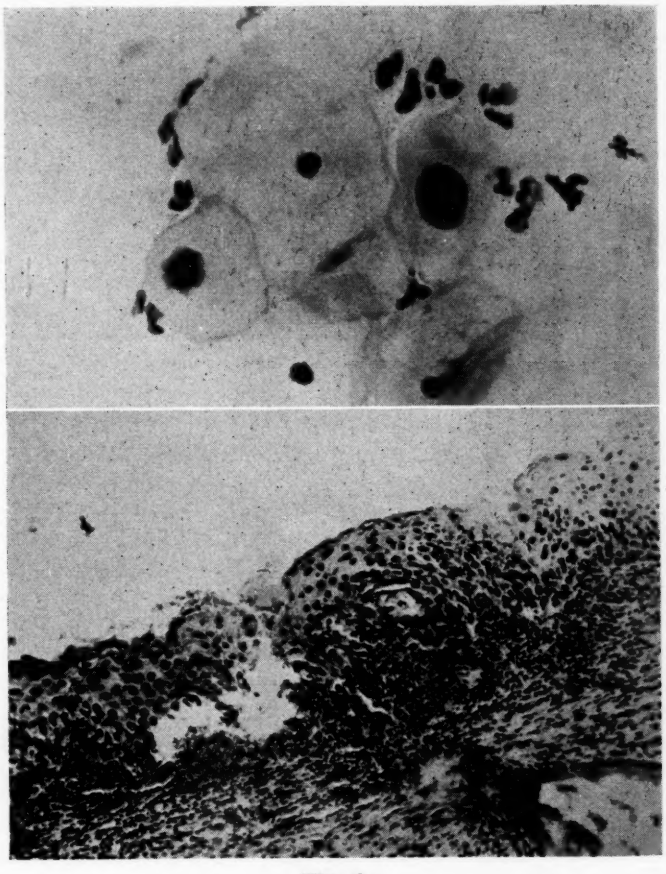

Fig. 6.

Fig. 5.—Endocervical smear. Note three normal cornified cells and two malignant cells one of which has a nucleus with ill-defined borders.

Fig. 6.—Microscopic section; same patient as Fig. 5. Preinvasive squamous-cell carcinoma of only one of numerous small sections of cervix obtained at biopsy.

cervices obtained by hysterectomy showed preinvasive cancer and that the average age of the patients was 36.6 years, the youngest being 23 and the oldest 53. Furthermore, it appeared that the transition from the preinvasive to the invasive phase may require an average of six years and that the appearance of clinical signs may be delayed an additional six years. Thus routine screening of all women by the endocervical smear technique should constitute an important part of preventive oncology.

Summary

The finding of a specific type of exfoliated malignant cells from preinvasive cancer is described and the morphology discussed.

In thirty of thirty-four cases of preinvasive cancer these specific cells were found, and in nineteen of twenty-one cases the diagnosis of preinvasive cancer was actually suspected and confirmed by biopsy.

Fig. 7.

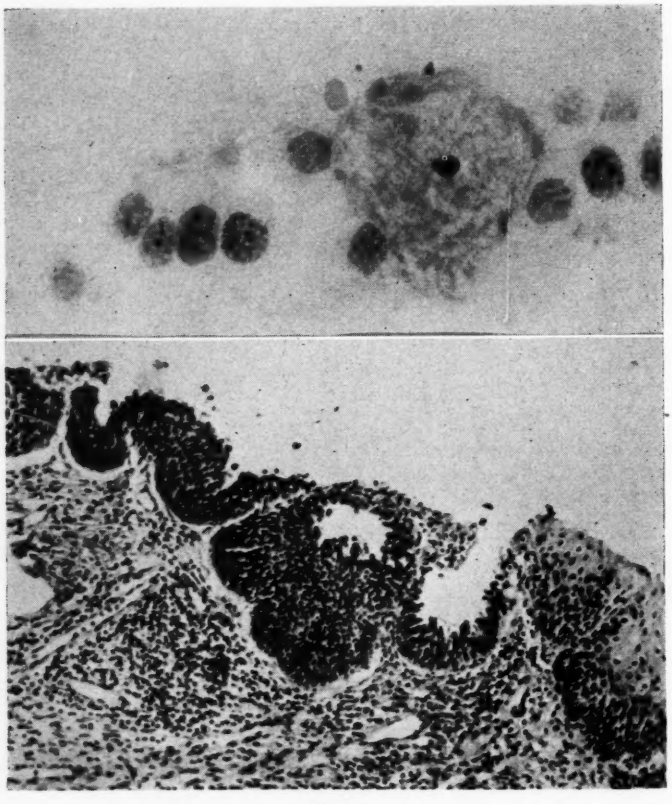

Fig. 8.

Fig. 7.—Endocervical smear. Note cancer cells with a particularly marked even granularity. The large cell in the center is a cornified cell.

Fig. 8.—Microscopic section; same patient as Fig. 7. Preinvasive squamous cell carcinoma in five of six sections of cervix obtained at hysterectomy.

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PAPILLARY CLEAR CELL ADENOCARCINOMA OF THE OVARY

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ARTHUR E. RAPPOPORT, M.D., YOUNGSTOWN, OHIO
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SINCE Schiller[1] first described mesonephroma ovarii in 1939, 46 cases have been reported in the literature, to our knowledge, and Schiller states that he has seen an additional 33 cases, making a total of 79.

The tumors are not characteristic grossly and vary from solid to cystic and papillary. Clinically, they produce no characteristic symptoms other than those which can be attributed to an abdominal mass. There is no abnormal uterine bleeding or evidence of any hormonal secretion or secondary sex changes. The age incidence in the reported cases has varied from 8 months to 72 years but generally they are seen past the age of 50. They may be benign or malignant.

We present two additional cases.

CASE 1.—Mrs. R. D., 65-year-old white woman, was admitted to the North Side Unit of the Youngstown Hospital Association March 13, 1948, complaining of gradual enlargement of the abdomen and generalized abdominal pain of six weeks' duration. She had lost 35 pounds in the past year. Her bowels had been irregular and frequent cathartics had been required. She had vaginal bleeding for four and one-half months, about fifteen years ago. She received x-ray therapy and she had had no vaginal bleeding or menstrual periods since.

Physical examination showed a markedly emaciated woman with a noticeable brownish pigmentation of the skin. No secondary sex characteristics were noted. The abdomen showed a fixed, tense, cystic, irregular mass which filled the pelvis, extended laterally into both flanks and superiorly to slightly above the umbilicus. Vaginal examination showed the cervix displaced high and anteriorly under the symphysis. At operation, on March 17, a large semisolid pelvic tumor mass occupying the area described above was found almost completely fixed on the left side. The omental vessels adherent to the tumor were markedly distended. The uterus, right tube, and ovary were small and atrophic. A bilateral salpingo-oophorectomy and panhysterectomy were done.

Gross Pathology.—The large tumor mass measured 20 by 19 by 9 cm., weighed 2,204 Gm., was nodular, yellow-orange, and was covered by a tough, white fibrous capsule (Figs. 1 and 2). It was semisolid to palpation. On section, it was composed of friable, yellow-orange nodules varying in size, with large cystic spaces measuring up to 8.5 cm. in diameter which were filled with bright red hemorrhagic clotted material.

Microscopic Findings.—The uterus, tubes, and right ovary are not remarkable. The sections from the left ovarian tumor show fairly uniform, cuboidal, moderately large cells with pale cytoplasm, sharply defined cell borders, moderately large nuclei with clumping of the chromatin. Nucleoli are especially prominent. The cells are arranged in sheets or nests (Fig. 3) but in many places line cystic spaces. Most of the cystic spaces have papillary projections covered by similar cells. In some of the larger cystic spaces, three or four papillary projections are seen, while others contain but one (Fig. 4). Some of the lumina contain exfoliated tumor cells, and cellular debris. The cells found in the solid nest are larger and of more irregular shape. Vascularization is prominent. Many large sinusoids are lined by tumor cells and filled with well-preserved blood. Necrosis and hemorrhage are prominent throughout the tumor and there is an associated lymphocytic and mononuclear cell infiltration

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Fig. 1.

Fig. 2.

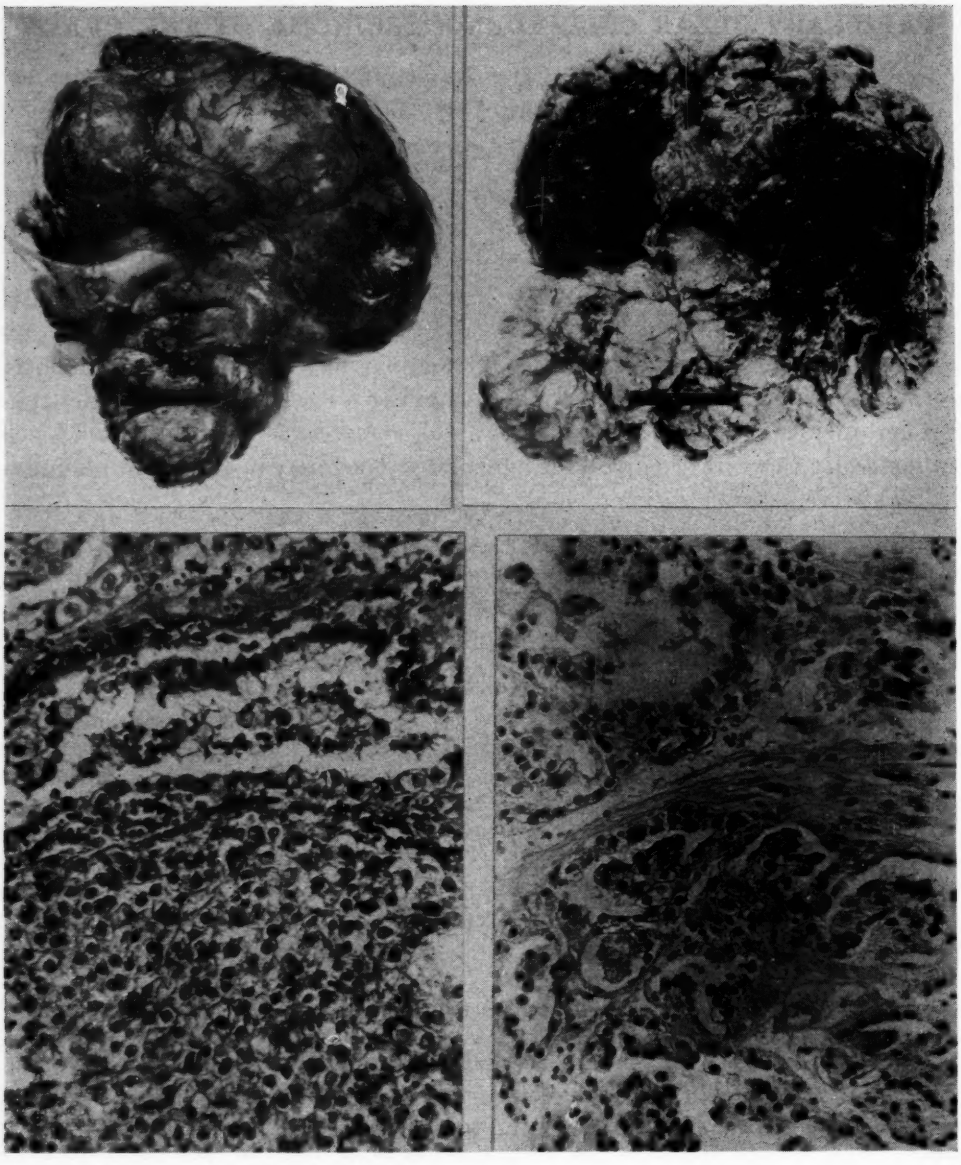


Fig. 3.

Fig. 4.

Fig. 1.—External view of uterus, tubes and left ovarian tumor. Ovarian tumor mass measured 20 by 19 by 9 cm., weighed 2,204 Gm.

Fig. 2.—Cut section of tumor showing yellow-orange nodules of varying size and multiple cystic spaces filled with bright red hemorrhagic material.

Fig. 3.—Photomicrograph of large clear cells arranged in solid nests. (×220)

Fig. 4.—Photomicrograph showing multiple cystic spaces lined by moderately large, clear cells showing papillary projections. (×220)

throughout the stroma. Masson's trichrome and Wilder's reticulum stains show a delicate reticular stroma. Mucicarmine stain fails to reveal mucin. Sudan IV stain shows most of the cells to contain small globules of fat. Abundant fat, however, is associated with the areas of severe necrosis.

The patient's postoperative course was uneventful. X-ray therapy was started six days after surgery and a full course was given. On follow-up six weeks postoperatively, no masses or tenderness were found. There was an area of ulceration in the left lateral vaginal wall which was thought to represent radiation necrosis. Papanicolaou stained vaginal smears were negative for tumor cells. Three months postoperatively this ulcerated area had regressed. The patient had no complaint and had gained 10 pounds in weight.

CASE 2.*—Mrs. S. W., 58-year-old white woman, was admitted to the North Side Unit of the Youngstown Hospital Association April 22, 1948, stating that she had noticed enlargement in the lower abdomen for eight months, which had become more marked in the last two months. She had had several episodes of "cystitis" characterized by frequency and burning. The burning cleared with "sulfa" drug but the frequency remained. For this reason she consulted a urologist who found a pelvic tumor. She denied any weight loss and stated her general health had been good. The past history was not pertinent. Her menstrual periods were formerly regular but she had not menstruated for 2 to 3 years.

Physical examination of the abdomen showed a large, fairly firm mass about the size of a grapefruit in the lower mid-abdomen. The mass was movable and slightly tender. No other organs were palpable. Pelvic examination revealed the cystic mass to be in the right adnexa. No secondary sex characteristics were noted. On April 24, under cyclopropane-curare anesthesia, a low midline incision was made. On opening the peritoneal cavity a large, deep purple, right ovarian mass was found. It was adherent to the right side of the pelvis and displaced the uterus against the bladder. The right tube was dilated. Bilateral salpingo-oophorectomy, hysterectomy, and appendectomy were done.

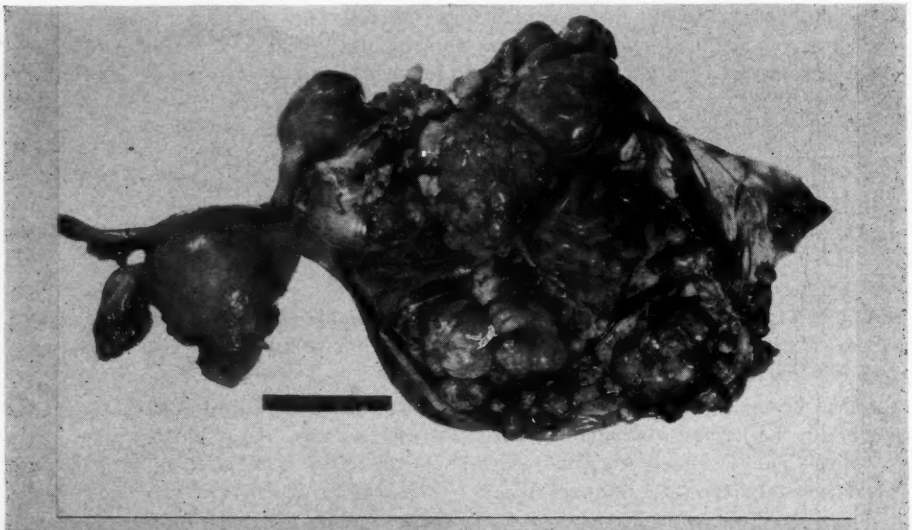
Gross Description.—The uterus, left tube, and ovary were essentially negative. The right tube measures 7 cm. in length and up to 8 mm. in diameter. The fimbriated end was bound densely to the large ovarian tumor and there was a small amount of red-brown material in the lumen. The right ovarian cystic mass measured about 22 cm. in its greatest diameter (Fig. 5). The external surface was blue-gray and smooth. It was filled with a thin, brown fluid. Arising from the inner wall of the cyst were numerous soft, yellow, polypoid projections, the largest of which measured 4 cm. in diameter.

Microscopic Findings.—The tumor shows numerous cystic spaces lined by low cuboidal epithelium with prominent and projecting nuclei. Nucleoli are inconspicuous. The nuclei show well-defined borders with irregularly clumped chromatin. The cell border is generally distinct, the cytoplasm clear and occasionally somewhat foamy. Many of the cysts are filled with pale pink, granular material which does not prove to be mucin on special staining. In other areas, the tumor shows solid nests of similar, although larger, cells. In other areas there are papillary projections into the lumina (Fig. 6). Here, the cytoplasm of the cell is basophilic and granular, while other places are covered by the same type of cells that lines the cystic spaces. Vascularization of these papillary projections is prominent. Sinusoids lined by tumor cells and filled with well-preserved red blood cells are seen. Necrosis is prominent throughout. Sudan IV stain shows small globules of fat in macrophagic cells in the interstitial tissues, and in many of the cells lining the cystic spaces. Fat is more prominent and found in larger globules in the areas associated with necrosis. Some areas demonstrate tubular structures lined by cells possessing basophilic and granular cytoplasm (Fig. 7). Masson's trichrome and Wilder's reticulum stains show scanty, loosely arranged, interstitial tissue with moderate vascularization. The right tube exhibits scarring of the plicated mucosa and wall. Some plicae are absent but the epithelium is uniform. Within the lumen in some zones one sees large numbers of very pleomorphic swollen cells with clear cytoplasm and dense hyperchromatic small nuclei.

*Acknowledgment is made to Dr. G. G. Nelson for this case.

The patient's postoperative course was uneventful and she was discharged on May 4, her tenth postoperative hospital day. One month after surgery the patient had no specific complaints. Pelvic examination showed no induration or masses. The patient is receiving x-ray therapy.

Fig. 5.



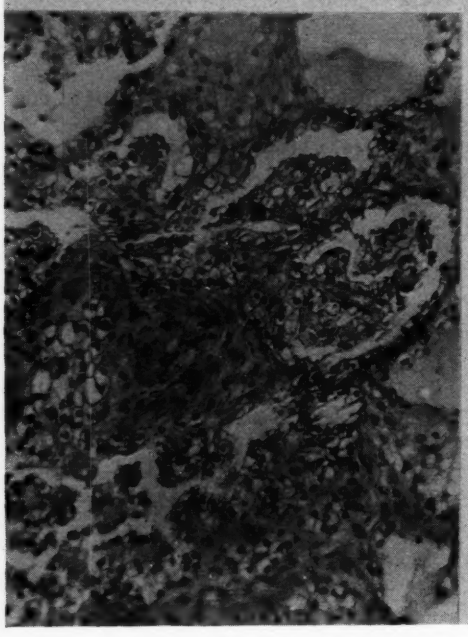


Fig. 6

Fig. 7.

Fig. 5.—External view of uterus, both tubes and left ovary. Cut section of the right ovarian cystic mass showing the multiple yellow, polypoid projections.

Fig. 6.—Photomicrograph showing multiple cystic spaces lined by moderately large clear cells with prominent and projecting nuclei. Papillary projections covered by similar cells are seen within the lumina. (×155)

Fig. 7.—Photomicrograph showing the tubule-like structure lined by cells with basophilic and granular cytoplasm. (×220)

Discussion

The varied terminology used to describe this tumor in the literature has depended upon the author's viewpoint. The gynecologist, who desires a classifi-

cation based on physiology and endocrinology, classifies it as a virilizing or non-virilizing lipoid cell tumor.[2] The embryologist classifies it as mesonephroma[1, 3] or a teratoid adenocystoma.[4] The morphologist classifies it as a papillary clear-cell adenocarcinoma.[5] The oncologist classifies it as a hypernephroid tumor.[6] We have no objections to the varied terminology applied, but we feel that the most important approach would be based upon the determination of the basic substrate from which the tumor arose.

Barzilai,[2] who has established a very satisfactory classification for ovarian tumors, has deviated from her original concept of relating the tumor to a specific cell origin and has thrown haphazardly into a single large category many tumors solely on a virilizing characteristic. This is of no value in classification but tends to confuse the issue, inasmuch as she includes such terms as hypernephroma, hypernephroid tumor of the ovary, adrenal tumor of the ovary, luteinoma, interstitioma and masculinovoblastoma under a single heading. She does, however, believe in an additional group separate from the above to which she has given the name mesonephroma in agreement with Schiller.

Stromme and Traut[4] believe that these tumors in question represent a teratoid adenocystoma and only in well-differentiated types are tumors seen which simulate the morphology of Schiller. These authors were likewise unable to demonstrate structures acceptable as glomeruli although papillary structures were abundantly present.

Schiller,[1, 3] in 1939, separated from a group of papillary ovarian tumors a group to which he gave the name mesonephroma ovarii, because, histologically, he felt these tumors were sufficiently different to justify a separate grouping. They possessed an epithelium which was generally flat, irregular with wavy lines, prominent projecting nuclei and thin rims of cytoplasm giving it a so-called button or hobnail-like appearance. The tumors are generally cystic with a tendency toward papillary projections into the lumina. The cells lining these spaces appear to resemble endothelium but where active proliferation was evident, it approached an epithelial form. These papillary projections possessed two or at most three capillary tufts and resembled the glomerulus of the mesonephric kidney.

Embryologically, the gonad is closely related to the mesonephric kidney and the adrenal gland. They are separated by the formation of the genital groove and separation is complete when the ovarian ligament is developed. Should the genital groove occur more peripherally, it is possible that some mesonephric elements might be included in the ovary. Inclusion of other tissues within the hilus of the ovary is known to occur. Islands of adrenal rests are recognized and Geist showed that after bilateral adrenalectomy a proliferation of these cells occurred in animals which survived. The reporting of these tumors in the testis, kidney, ovarian ligament, and associated with other ovarian tumors such as dermoid and embryoma would definitely suggest a disturbance in the usual embryological mechanisms.

We feel that the mesonephric origin of these tumors can be questioned. The true Wolffian duct tumors[7] are generally retroperitoneal or intramesenteric and these tumors show glomeruli and tubules. In the mesonephroma, the glomerular structures are generally scarce and poorly developed and tubules are absent. Schiller,[1] by preparing serial reproductions of these papillary structures, felt that he definitely proved their glomerular nature. Kazancigil and co-workers,[8] however, attempted to reproduce Schiller's work but were unsuccessful. The variation seen in the epithelium from flat to cuboidal or low columnar is the picture seen in the mesonephric glomerulus, however. Tubules in these tumors are rare. Why they are not found has never been satisfactorily explained. Schiller suggests that the rarity may be due to the fact that the Wolffian duct is not close enough to stimulate tubule formation.

Kazancigil and co-workers[8] preferred to classify these tumors as papilloendotheliomas. These authors felt that there was a definite endothelial character in the arrangement of the tumor cells, which assumed an angiomatous and cavernomatous appearance in one of their cases, and an angio-endotheliomatous picture in another case with foci of hematopoiesis. This, they thought, might indicate a primitive angioblastic mesenchymal reaction.

Saphir and Lockner,[6] on the basis of two cases examined, leaned toward Schiller's conception in order to explain the origin of these tumors. However, as a pathologist, he proposes a purely descriptive anatomical diagnosis of adenocarcinoma with clear cells (hypernephroid) of the ovary which implies that this is synonomous with mesonephroma.

Jones and Seegar[9] report six cases in a paper entitled "Mesonephroma of the Ovary." Their conclusions hardly support the validity of this title, inasmuch as they believe that true glomeruli were not present. In a later paper,[10] these authors were not able to supply any further data which might elucidate this question, thus leaving the origin unsettled.

In attempting to establish a histiogenetic classification of ovarian tumors, Spencer and Reel[11] considered the possibility of mesonephroma. This is on theoretic ground and they offer no conclusive proof other than Schiller's work to support this contention.

Schiller[12] has stated that he had never seen a primary carcinoma of the ovary, but that they always arose in benign tumors. The origin of one of our tumors could have been in a papillary cystadenoma of the ovary. We would disagree with Stromme and Traut[4] who state that their tumors produced mucin and for this reason would not consider a serous cystadenoma origin. In contrast to their cases, our tumors failed to show mucin. We would agree with Stromme, however, that probably these tumors are not as clearly defined a group as was originally outlined by Schiller.

That these tumors are mesonephric in origin has been accepted by several authors, and such a terminology has been used by the Ovarian Tumor Registry.[13] While this approach is commendable, for we must begin to classify tumors on an embryologic basis, the acceptance of this concept, we believe, has occurred on scanty proof. Although our cases do not exactly fit Schiller's original description, we do feel they are similar. The two tumors did show epithelium which resembled that described by Schiller in his original work. However, we did not demonstrate mesonephric glomeruli. The papillary projections into the cystic spaces contain capillaries but the resemblance to glomeruli is difficult to recognize. In many cystic spaces there were three or four papillary projections and a few cystic spaces were seen which had only one. One should expect papillary projections into cystic spaces in a rapidly growing neoplasm. In malignant tumors, however, one should not expect an exact reproduction of a structure as complex as a glomerulus since dedifferentiation is a feature of neoplasms.

Novak,[5] who examined slides from our two cases, states he feels Schiller's mesonephroma often represents only a variant of adenocarcinoma. In both our cases, he felt the prevailing picture was that of a clear-cell adenocarcinoma.

The proof of the glomerular nature of these papillary projections, we believe, should depend upon very definite anatomic criteria. A well-formed Bowman's capsule should be identified. The glomerular tufts should be distinct with well-formed capillaries lined by endothelium and with a definite basement membrane and a tubular connection to the glomerulus should be found. Equally important, their functional nature should be ascertained. In reviewing the literature, we have been unable to find satisfactory proof of any of these morphologic criteria. No comment has been made, to our knowledge, of physiologic activity of these glomeruli. If we assume them to be true glomeruli, certainly

a uriniferous filtrate should be produced. Since excretory tubules are absent, should we not expect accumulation of the filtrate with the formation of cysts similar to the retention cyst of the adult kidney?

It does not seem wise to introduce into our thinking of ovarian tumors a concept which parallels that used in the hypernephroma of the kidney. The tremendous amount of work with the paucity of positive results in the renal tumor, should be a warning against transferring the type of reasoning originally used by Grawitz, to this ovarian tumor.

Summary and Conclusions

1. Two yellow nonvirilizing tumors of the ovary occurring with no specific symptoms are reported.

2. One tumor was solid, the other was papillary and cystic.

3. Microscopically, they showed moderately large, clear, lipoid-containing cells arranged in solid nests and lining cystic spaces showing papillary projections.

4. The mesonephric origin of these two tumors could not be accepted as proved.

Acknowledgment is made to Dr. Horace K. Giffen for help and criticism, to Mrs. Mary Miles for the photographic reproductions, and to Miss Millie Sokol for compiling material.

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THE "CRUSH" SYNDROME IN OBSTETRICS AND GYNECOLOGY*

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THE crush syndrome is part of a general syndrome of urinary suppression and azotemia; it is not caused by kidney disease and, therefore, is of extrarenal origin.

This general syndrome has been designated as lower nephron nephrosis by Lucke[1] and as acute tubular disease and acute toxic nephrosis by Moon.[2] It follows a variety of causes of which the following have been noted: shock (either traumatic or operative), transfusion reactions, burns, medical diseases associated with dehydration or marked hypotension, such as is found in severe infections or at the end of a chronic debilitating disease, toxic poisoning, and heat stroke.

A complete review of the literature will be found in studies by Lucke,[1] Moon,[2] Martineau and Hartman,[3] Corcoran and Page,[4] and Bell and Knutson.[5]

The crush syndrome refers specifically to posttraumatic anuria and consists of the initial tissue damage or injury followed by shock which may be severe, moderate, or at times absent; then sudden urinary suppression. That urine which is passed is scanty, acid, of low specific gravity, colored red or brown with myoglobin, and contains pigmented casts, leucocytes, and albumin. Meanwhile, azotemia appears, as shown by increasing blood urea nitrogen; the patient becomes restless, with thirst and vomiting, and between the fifth and ninth days dies or starts to recover spontaneously. If recovery ensues there is apparently no permanent renal damage.

Pathology

There are two groups or related states of renal injury: first, those in which the principal lesion is the obstruction of the renal tubules by pigmented (myoglobin, hemoglobin) casts; and, second, those in which the injury lies principally in necrosis of the epithelium of the distal convoluted tubules. The underlying mechanism in all these changes is not clearly understood but seems to occur in the following sequence: the initial injury causes a stimulation of the renal vasomotor nerves which in turn causes a renal ischemia by constriction of the cortical interlobular arteries and diversion of blood into the medulla. This causes oliguria and aciduria which facilitates the precipitation of pigmented casts and necrosis of the tubular epithelium. The damage to the tubular epithelium allows the urinary filtrate to be reabsorbed into the circulation by a process of diffusion. Thus, the oliguria or anuria is produced by the interruption of renal secretion.

James Young[6] of London first reported this syndrome in connection with obstetrical injuries and the authors,[7] in a previous paper, reported three cases, two of obstetrical origin and one a twisted ovarian cyst. In the present paper we have reviewed all the maternal deaths in the city of Philadelphia from Jan. 1, 1930, to Dec. 31, 1946. This material was obtained from the records of the Maternal Mortality Committee of the Philadelphia County Medical Society. From this series of fatal cases totaling 2,000 in number we found five deaths that showed the characteristic syndrome of urinary suppression following trauma. Adding these to the three cases from the previous paper, we are reporting a total of eight cases; six maternal deaths, one ruptured uterus with recovery, and one twisted, infarcted ovarian cyst with recovery.

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Report of Cases

CASE 1.—*Placenta Abruptio:* J. I., 40 years old and pregnant about 28 weeks, who showed mild hypertension throughout pregnancy and slight albuminuria during the preceding month, developed placenta abruptio. One hour later she was brought to the hospital and five and one-half hours later was operated upon. A typical Couvelaire uterus was found with retroplacental blood clots, infiltration of uterus and broad ligaments.

A classic cesarean section was performed and the patient was given one blood transfusion and fluids postoperatively. A typical urinary suppression followed, terminating in death on the fifth postpartum day. Autopsy showed toxic nephrosis of the kidneys with chronic glomerular nephritis and necrosis of spleen.

CASE 2.—*Placenta Abruptio:* S. M., 18 years old, a gravida i at term, developed moderate hypertension, 160/110, and albuminuria. Four days later placental separation began; first with pain and, eight hours later, bleeding. Three hours later she was admitted to the hospital in active labor and conservative treatment was administered in the form of morphine, puncture of membranes, and manual dilatation of cervix. Delivery was spontaneous about 24 hours after the onset of symptoms. The baby weighed 4,080 Gm., was full term and stillborn.

The placenta showed that two-thirds had separated prematurely. The blood loss was measured as 500 c.c. intrapartum and 350 c.c. postpartum. In addition the blood loss before admission added to the total. The patient received one transfusion of 350 c.c. post partum. Following delivery, she developed the typical symptoms of urinary suppression and azotemia and died three days post partum. Autopsy showed renal tubular necrosis and glomerular ischemia.

CASE 3.—*Placenta Abruptio:* (Reported in previous paper.) M. C., 29 years of age, gravida ii, was admitted to the hospital at 28 weeks of pregnancy for hypertensive disease and pre-eclampsia. After a week of conservative treatment placenta abruptio suddenly developed with a blood loss of about 300 c.c. and no shock. This was treated by prompt cesarean section and transfusion of 500 c.c. Immediately following operation the patient developed urinary suppression and azotemia. Urinary output began to return on the eleventh and twelfth postpartum days, but she suddenly died on the thirteenth day. Autopsy showed a typical lower nephron nephrosis with pigmented casts.

CASE 4.—*Tubal Pregnancy:* E. L., 46 years of age, gravida iv, was admitted to the hospital. There were no signs of shock or anemia. The next day she was operated upon. The findings were a lacerated cervix, fibroids of the uterus, cystic ovaries, right hydrosalpinx, left tubal pregnancy, and hemorrhoids. The operation consisted of a curettage, a trachelorrhaphy, hemorrhoidectomy, multiple myomectomies, and a bilateral salpingectomy. Following the operation the patient developed urinary suppression with oliguria and died on the third postoperative day. There was no autopsy.

CASE 5.—*Tubal Pregnancy:* M. M., aged 31 years, gravida viii, was admitted to the hospital and operated upon promptly for tubal abortion. The pelvis was found to be full of blood. The operation consisted of a left salpingo-oophorectomy; the patient was given a transfusion of 600 c.c. and parenteral fluids. Following the operation she developed urinary suppression and paralysis of the left arm and leg. Both these conditions persisted until death. The final note on the chart was, "Patient was thrown into acute renal shutdown by the trauma of the tubal abortion." Autopsy showed tubular degeneration of recent origin. The brain showed an infarct of the right frontoparietal region.

CASE 6.—*Rupture of Uterus:* (Reported in previous paper.) R. B., aged 25 years, gravida iv, with breech presentation and slow, difficult labor, was given sedation after 29 hours of poor pains. Eleven hours later, although the cervix was only partly dilated, she was given Pitocin 0.15 c.c. which produced rupture of the uterus. A consultant delivered the baby and placenta, recognized the ruptured uterus and promptly performed a hysterectomy. A tear extended up the right side of the uterus to the fundus with about 300 c.c. of blood in the

peritoneal cavity. The patient received seven blood transfusions and had a stormy convalescence. Urinary suppression occurred the first two days and then began to improve. The blood urea nitrogen reached a maximum of 56.5 mg. per cent on the fourth day post partum but returned to normal two days later. The patient eventually recovered and was discharged on the forty-second day post partum.

CASE 7.—*Rupture of Uterus:* G. G., aged 32 years, a secundigravida, began labor at term with a breech presentation due to an unrecognized hydrocephalic monster. After twenty-four hours of difficult labor, extraction was attempted. The body was delivered but the head obstructed. Eventually the baby was delivered by craniotomy after a great deal of manipulation. Immediately following the delivery the uterus was found to be ruptured by a tear extending from the cervix to the fundus. Abdominal operation showed free blood in the peritoneum and the rent was sutured without hysterectomy. The patient received a blood transfusion. Urinary suppression with nitrogen retention developed immediately and she died on the sixth day post partum with the characteristic symptoms of lower nephron nephrosis.

CASE 8.—*Twisted Ovarian Cyst:* (Reported in previous paper.) R. Z., a woman 22 years of age, was suddenly seized with pain during a normal menstrual period. This marks the twisting of the cyst with infarction or the initial trauma. Immediately urinary suppression developed. Pain and urinary suppression persisted for four days but the patient remained at home against the advice of her physician. Finally, she was admitted to the hospital with a diagnosis of left renal calculus producing urinary obstruction with reflex anuria of opposite side. Cystoscopic studies were negative except for the passage of a little reddish-brown urine. Finally on the sixth day after the twisting of the cyst, urinary output began to increase and the patient to improve. Further studies revealed a large tumor in the abdomen, high on the left side. Operation performed twenty-six days after the original accident showed the cyst to be twisted three times on its pedicle, infarcted, with bloody extravasation into the cyst wall. The recovery was uneventful.

Comment

All of this group of cases show the same sequence: first, trauma, either accidental or surgical, followed by urinary suppression and azotemia. It is possible that, in some cases, the syndrome may have been caused by unrecognized incompatible blood transfusion reactions; but the hospital records were studied with care and we believe that each case reported is authentic. Six of the eight cases received blood; none was given in the case of tubal abortion and multiple operations or in the case of twisted ovarian cyst.

If the treatment for shock is delayed or is inadequate the renal damage soon progresses to the degree that it cannot be controlled and the disease must run its inevitable course ending in death or recovery. It is well known that the best treatment for shock is blood transfusion, which should be given early and often. In this study, we believe that six of the eight cases were treated inadequately by transfusion: five received only one transfusion and one received none. Of the two cases with recovery, transfusion was not indicated in one (the twisted cyst) at the time of admission to the hospital, and the patient with ruptured uterus received seven transfusions, starting as soon as the rupture was discovered. The use of these transfusions early and frequently may have been the deciding factor in preventing extensive renal damage.

The treatment of "crush syndrome" begins with prevention. First: prevent obstetrical errors, chiefly birth trauma following dystocia. The two cases of ruptured uterus are examples of faulty judgment. In the first case, the error lay in failure to recognize hydrocephalus and in an improperly performed destructive operation. In the second case, the administration of pituitary extract during the first stage of labor caused a disaster that was almost fatal. Second: prevent shock or, if it occurs, treat it promptly and adequately. As was men-

tioned earlier, shock causes vasoconstrictive renal ischemia. This ischemia leads to oliguria, which, associated with aciduria, predisposes to precipitation of pigment casts. In the presence of such renal ischemia, myoglobinuria and hemoglobinuria, which cause little injury under normal conditions, result in severe renal injuries (Corcoran and Page).

Once the urinary suppression is established, treatment is directed toward control of the pathologic physiology. However, the renewed interest in this neglected syndrome has been so recent that the therapy offered has not been fully proved or, in the case of nerve block, even tried. There are three therapeutic procedures that seem to offer good prospects of success, namely: urinary alkalinization, peritoneal dialysis, and nerve block (splanchnic, high spinal, or caudal anesthesia).

Urinary alkalinization, including the use of a diuretic, has been widely studied and definitely decreases the degree of renal injury. Sixth molar sodium lactate is the best preparation, in a dosage of one or more liters daily for alkalinization and the best diuretics found so far have been sucrose or mannitol in repeated doses of 5 to 10 Gm. (0.1 Gm. per kg. of body weight), or sodium sulfate (1 Gm. intravenously). Alkaline therapy, so far, has proved of only slight aid and, in fact, it may be possible for an injured kidney to form alkaline urine, so that if the treatment is pushed too far alkalosis may result.

Peritoneal dialysis as a method of removing nitrogenous compounds during the period of renal damage may keep the patient alive until sufficient renal regeneration has occurred. This procedure is based on the fact that the peritoneum is an excellent osmotic membrane, rich in blood supply with a large surface. Flushing it with properly prepared fluids will remove considerable quantities of nitrogenous products. One of us has used this technique successfully in a case of severe transfusion reaction. However, more experience is needed before its usefulness can be evaluated properly.

Splanchnic block, high caudal, or spinal anesthesia has been suggested by Franklin et al.[10] as a method of combating the stimulation of the renal vasomotor nerves which in turn causes the renal ischemia. The authors have had no experience with this procedure but it seems logical and well worth a trial.

Summary

In a review of the maternal deaths in Philadelphia since the formation of the Maternal Mortality Committee of the County Medical Society seven maternal deaths were found which showed the "crush syndrome" with lower nephron nephrosis. An additional case of twisted ovarian cyst is included in the report. The obstetrical cases included placenta abruptio, ectopic, and birth trauma. Particular stress is placed on prevention of shock or its treatment by early and frequent blood transfusions.

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PULMONARY MUCORMYCOSIS COMPLICATING PREGNANCY

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THE obstetrician sets out to deliver a woman successfully of a normal living infant. To accomplish this, he must be on the alert for all possible abnormal signs and symptoms that occur during gestation.

Nausea and vomiting occurring in the third trimester, outside of possible impending eclampsia, usually are associated with other serious conditions, such as appendicitis, intestinal obstruction, peptic and duodenal ulcers, and hyperthyroidism.[1] Other rare conditions are also complicated by nausea and vomiting. As an example, we are presenting a case history of what we believe to be the first case of mucormycosis infection complicating pregnancy, in which the initial complaints were intractible nausea and vomiting.

This 26-year-old Negro para i (Hospital Admission No. 125942), due by dates on June 27, 1947, was first seen for this pregnancy on Nov. 4, 1946, when she was six and one-half weeks pregnant, her last menstrual period having been Sept. 20, 1946. Her initial examination was essentially normal. However, a brown reduction for sugar was noted on her admission urinalysis. Her past surgical history was negative. Her past medical history revealed pneumonia as a child. A positive Wassermann test had been discovered in another clinic in June, 1946, and the patient subsequently had been given penicillin in three daily doses of unknown amount for nine days. Following this, two serological examinations for syphilis were reported negative. The patient ran a normal prenatal course up to 28 weeks' gestation, with a gradual increase in weight from 119 pounds to 130½ pounds. She had a normal blood pressure on her last clinic visit on March 24, 1947. All urine examinations were negative with the exception of a second brown reduction for sugar found at 24 weeks' gestation.

On March 31, 1947, at 29 weeks' gestation, she was admitted to the Boston Lying-in Hospital with a history of upper respiratory infection and cough of one week's duration. Four days before admission, severe epigastric, cramplike pains "coming in waves" developed and were unrelieved by antacids prescribed by her local physician. On the day before admission, the pains increased and intractible vomiting ensued.

Physical examination revealed a thin, lethargic, markedly dehydrated, Negro woman in some abdominal distress. She had lost 13½ pounds since her last clinic visit on March 24th, which was a week before admission. She was difficult to arouse but would respond to painful stimuli. The ears, eyes, nose, and throat were negative. The chest was clear to x-ray. There was slight tenderness and spasm in the epigastrium. The uterus was enlarged to approximately 26 weeks' size and nontender. No other abdominal masses were palpable. Rectally, the cervix was not well made out, although a breech was thought to be presenting. Temperature, pulse, and respiration were normal. Urinalysis revealed one plus albumin, 2 plus diacetic and acetone, with granular casts. Blood pressure was 134/70. Initial blood count revealed a hemoglobin of 70 per cent, white blood count of 9,700 and red blood count of 4.1 million. Sedimentation rate was 2 mm./hr. Icteric index—2.

The patient was treated for her dehydration during the first forty-eight hours but showed no improvement. It became obvious, therefore, that her problem was more than that

of severe vomiting at the 26th week of pregnancy. Her urine albumin gradually rose from one plus to three plus on the day of her death. The various blood and urine studies during the course of hospitalization are presented in Table I.

TABLE I. LABORATORY DATA

Urine

DATE	ALBUMIN	SUGAR	DIACETIC	ACETONE
March 31	1 plus	0	2 plus	2 plus
April 2	2 plus	Br. Red		1 plus
April 3	1 plus	Br. Red		1 plus
April 4	1 plus			
April 5	2 plus	Br. Red		0
April 6	3 plus	Green with sediment		0

Blood

DATE	CO_2 COMB. POWER	T. P.	NPN	BL. SUGAR	CHLORIDES	HGB. PER CENT	RBC	WBC
March 31						70	4.10 M	9,700
April 2	38 vol. %		56	247 mg. %		118	5.05	10,900
April 3	20 vol. %	4.9	68	282 mg. %	114m/Eq/L	110	5.01	9,600
April 4	36 vol. %	4.2	67	270				
April 5	36 vol. %		104	300		117	4.96	6,800
April 6		4.2	88	252		99	3.400	9,300

On the third hospital day the patient became more drowsy, despite intravenous fluids. Her blood pressure rose to 170/80. The neurological signs were negative. A lumbar puncture was performed, revealing an initial pressure of 190 mm. of water with normal dynamics and pulse wave. The fluid was clear, protein 8.4 mg. per cent. There were no cells and the Hinton test was negative. On the fourth hospital day, because of increasing stupor, the neurological consultant stated: "The patient is stuporous without lateralizing neurological signs. The most likely explanation of this condition is the acidosis and uremia. There are no signs at present of focal brain disease, though these could be masked by the stupor." Because of the stupor and lack of lateralizing neurological signs of a brain lesion, the consultant made a diagnosis of diabetes mellitus, and renal disease of undetermined type. (Two cephalin-flocculation tests for liver damage were negative.) Laboratory data are summarized in Table I.

On the fifth hospital day the patient apparently started up in labor, and simultaneously developed a temperature of 100.8° F. (R) for the first time. A sterile pelvic examination was performed and the cervix was found to be two fingers dilated; accordingly, a foot was brought through the cervix and a fillet attached. This was done in the hope of shortening labor and perhaps easing the load on the kidneys. One hour and twenty minutes later the patient delivered herself of a 2 pound, 4½ ounce macerated stillborn male infant. The placenta was delivered uneventfully.

Following delivery, the temperature rose to 103.2° F. (R). Respirations continued to rise to 45 per minute. The patient failed to improve and died on April 7, 32 hours post partum, seven days after admission to the hospital, and thirteen days after the onset of symptoms.

An abstract of the pathologic report follows:

Gross.—The body was that of a well-developed, fairly well-nourished, Negro woman measuring 66 inches in length.

The peritoneal cavity contained about 50 c.c. of clear, golden-yellow fluid, although the serosal surfaces were not remarkable. Inspection of the organs in situ revealed essentially normal finidngs, except for a spleen which was slightly smaller than normal and a ptotic loop of transverse colon. There was a bright reddish-purple, boggy, postpartum uterus extending 12 cm. above the symphysis. The pelvic organs were otherwise not remarkable.

The right pleural cavity contained 800 c.c. of brownish, cloudy, purulent, slightly foul-smelling fluid. The pleural surfaces were red and injected, with numerous soft, stringy, friable, fibrinous adhesions from the right upper lobe to the parietal pleural surface, especially posteriorly. There were no adhesions or fluid in the left pleural cavity.

The pericardial cavity contained about 50 c.c. of clear, golden-yellow fluid and showed negative serosal surfaces.

The lungs weighed as follows: right lung, 520 Gm.; left lung, 340 Gm. The right lung was of normal size and shape. The pleural surfaces were somewhat dull, pinkish red to purple in color, with filmy fibrinous adhesions on the upper lobe, most marked posteriorly. The upper lobe was rubbery in consistency. On the pleural surface, there were scattered fine cystic blebs measuring approximately 0.1 cm. in diameter, none of which was ruptured. The cut surfaces of the right upper lobe showed a red, homogeneous, wet surface which oozed large amounts of fluid on pressure. The medial aspect of the right upper lobe just above the interlobar fissure revealed a black, homogeneous localized area of softening occupying about one-third of the lobe, which was in contrast to the firm surrounding red area. The right lower and middle lobes were of a dark red color and had a wet red surface which oozed large amounts of fluid on pressure. The whole lung was subcrepitant to firm in consistency, the upper lobe giving an impression of early consolidation, the middle and lower lobes giving an impression more consistent with atelectasis, congestion, and edema. The pulmonary vessels were dissected to their third and fourth branches. A questionable firm reddish-yellow thrombus was noted at the second bifurcation of the right lower lobe vessel. After formalin fixation, a moderate-sized gray, friable, adherent thrombus was found in the artery leading to the softened area in the right upper lobe.

The pleural surfaces of the left lung were pinkish red in color, the consistency being subcrepitant throughout. The cut surfaces showed a reddish purple surface which oozed a moderate amount of frothy, bloody fluid. The pulmonary vessels were not remarkable and contained no thrombi.

The bronchial mucosa was a deep reddish pink color and markedly edematous. The lumen contained a moderate to marked amount of tenacious, reddish-gray, mucopurulent material. The hilar lymph nodes showed moderate anthracotic pigmentation.

The remainder of the gross findings were not remarkable. Dissection of the neck revealed no evident abnormality.

The brain weighed 1125 Gm. The arachnoid was clear, moist, and glistening. There was no adherence to the cortex and no evidence of meningitis or tuberculosis. The brain was symmetrical and of normal consistency. The convolutions were of the normal pattern and the sulci were of normal depth. The vessels were not remarkable.

Microscopic.—Eighteen sections of lung were examined. The majority of them showed the usual architecture. The alveoli were generally well expanded. There was only moderate focal atelectasis, moderate amount of cellular debris and edema fluid in the alveoli. There were some small, fibrin thrombi in the arteries which, in general, were moderately congested. The alveolar capillaries also were engorged. In a number of focal areas, collections of polymorphonuclear leucocytes and strands of fibrin in the alveoli were suggestive of early bronchopneumonia. There were also some edema and acute inflammatory cellular infiltration of the pleura in these areas as well. Numerous sections were taken from the soft black homogeneous area of the right upper lobe, and showed an unusual mycotic organism on examination. In the lung tissue showing marked invasion by the mycelia, there was preservation of the alveolar pattern but the cellular detail was very blurred. The alveoli, for the most part, were outlined by eosinophilic granular material without cellular detail and by hemosiderin which outlined the position of the alveolar capillaries. There was abundance of cellular debris and edema fluid in the alveolar spaces. The pleura was markedly thickened and edematous. There was a fibropurulent exudate on the surface containing many polymorphonuclear neutrophiles. Numerous large, tubular structures with thin basophilic staining walls could be seen, in which very rare septae were present. There was marked branching of the hyphae which seemed to contain a coarse, granular, basophilic material. (See Figure 1, *A*, *B*, *C*.) Occa-

sional multinucleated cells were noted. The mycelial structures were very numerous and were present both in the pleura and underlying lung tissue. One section showed a definite, recent, pulmonary infarct with the characteristic microscopic findings. Section of the pulmonary artery supplying the area of the infarct showed a large, antemortem thrombus with massive invasion of the the thrombus and of the vessel walls by mycelial hyphae. Numerous other sections of lung show findings consistent with marked pulmonary edema and moderate pulmonary emphysema.

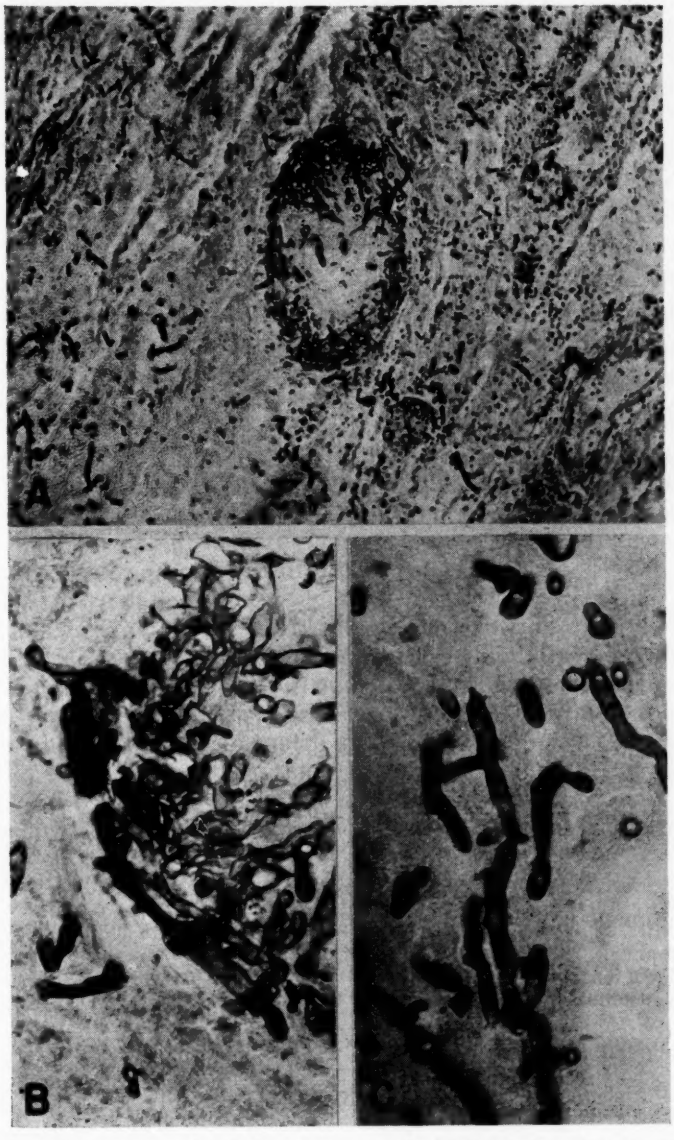

Fig. 1.—*A.* Shows massive invasion of lung and thrombosis of vein by mycelia. (100×).
B. Shows high power view of vein in Fig. 1*A*, demonstrating infrequent septation and branching of the mycelial structures. (400×).
C. Shows numerous branching of hyphae with infrequent septation in necrotic lung tissue. (400×).

Two sections of pancreas showed the usual irregular lobular arrangement of small compact acini. There was no evidence of the pathological findings which are usually felt to be consistent with diabetes.

Sections of liver, spleen, kidney, bladder, breast, and thyroid were not remarkable.

All the pathological sections, including the brain and placenta, were carefully examined for the presence of mycelial hyphae and none were found except in the sections of the lung.

Cultures of right pleural fluid, lungs, pericardial fluid, and heart blood, were planted on routine blood agar plates, thioglycollate and broth. All these cultures showed only growth of *Bacillus coli* and *Staphylococcus aureus.* Fungus infection was not suspected and therefore no suitable cultures for its detection were planted.

Dr. C. W. Emmons,[2] Principal Mycologist, U. S. Public Health Service, kindly reviewed sections of the lung and has allowed us to quote his letter as follows:

> "Since cultures were not made, the fungus cannot be positively identified. I agree with your opinion that it is probably Mucor. The size of the hyphae, profusion and type of branching, infrequent septation, and multinucleate cells are consistent with that fungus, and in these respects there is a resemblance to similar structures in material from other cases I have seen which were provisionally diagnosed as mucormycosis."

Discussion

Mucormycosis is, indeed, a rare disease in man. These fungi are of the Class of Phycomycetes, order Mucorales, in the family of Mucoracea, which is parasitic in animals and man. Gregory, Golden, and Haymaker,[3] in 1943, reviewed the subject and reported three cases of mucormycosis involving the central nervous system, the original cases being characterized by a triad of infection of the orbit, uncontrollable diabetes and the presence of mucor mycelia in thrombosed cerebral vessels. LeCompte and Meissner[4] added a fourth case involving the central nervous system and demonstrated the typical triad. There have been ten cases reported in the literature involving the lung only,[3] this location being the most common; the central nervous system the least common.

This case is of interest because of the initial complaints of intractible nausea, vomiting, and pain in the third trimester of pregnancy. During her prenatal course she had on two occasions a brown reduction for sugar which was never thoroughly investigated. The question naturally arises: Did this patient have mild, uncontrollable diabetes and subsequently became infected by a fungus which found a fertile field for growth? This question is unanswerable, although one cannot help but wonder if, had more attention been directed to this isolated urinary finding early in pregnancy, this maternal death might have been prevented. It is presented to stimulate consideration of obscure infection, such as mycosis, in unexplained nausea and vomiting in the third trimester of pregnancy.

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THE SPECIFIC TREATMENT OF VAGINAL MYCOSIS

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VAGINAL mycosis continues to be an annoying problem even with all the innumerable agents which are available to the physician today. The causative organisms belong to the medical monilia group known commonly as *Monilia albicans* or *Candida albicans.*[1] These fungi are frequently found in the mouth, vagina, and intestinal tract of the normal individual.

Vaginal mycosis occurs predominantly during pregnancy. It is assumed that the increased amount of glycogen-like material present during gestation favors the growth of the *Candida albicans.* Exceptions to this will be found in patients in whom the common sugars (lactose excluded) are used for vaginal trichomoniasis therapy, or in postmenopausal individuals on excessive estrogenic therapy. Diabetes is another predisposing factor because the infection is related directly to the glycosuria, and thus it will be encountered ordinarily in the uncontrolled diabetic patient. The symptoms in the gravid patient disappear immediately after delivery. Fungi may be isolated from the vagina in 14 to 41 per cent of patients depending upon the type studied.[3] It is conservative to estimate that 25 per cent of all pregnant patients harbor these fungi in the vagina. A fair percentage of the group will develop mycosis. The sporadic case of oral thrush is most likely the result of oral contamination during delivery. From these facts it is evident that these organisms are opportunists.

One of the patients in our Out-Patient Clinic reported the symptomatic improvement of her vaginal mycosis following use of a contraceptive jelly. This led Hesseltine[2] to a thorough investigation of all the ingredients of this jelly against a medical monilia (No. 6225). The technique of Hesseltine and Hopkins[4] was employed. Through this work it was found that ricinoleic acid held promise as a fungicide for the medical monilia. The buffered acid (pH 4.5) jelly was found to be nonfungicidal.

Ricinoleic Acid and Salts

A study was instituted to evaluate the practical application of ricinoleic acid in the treatment of vaginal mycosis. A tragacanth-acacia buffered jelly was used as the vehicle for the ricinoleic acid. The concentrations investigated were 0.75 per cent, 1.5 per cent, 2 per cent, and 3 per cent. All concentrations in vitro revealed fungicidal behavior.

On pilot studies, 3 per cent ricinoleic acid was tolerated satisfactorily. It gave relief more quickly than the weaker concentrations and the commercial contraceptive jelly which contained 0.75 per cent ricinoleic acid. It is believed that the ricinoleic acid could be equally effective if used in some other type of vehicle, such as a vaginal suppository.

Larson and his co-workers,[5, 6, 7] as well as Reasoner[8] and Spencer,[9] have done some investigative work on the sodium salt of ricinoleic acid. Larson et al., in their studies of the effect of surface tension of the menstruum upon bacteria and toxins, have shown that virulent strains of organisms *(Bacillus tuberculosis, Diplococcus pneumoniae,* and *Streptococcus viridans)* can be rendered nonvirulent when suspended in solutions of sodium ricinoleate. Larson is of the belief that the soap, by lowering the surface tension of the menstruum, causes the bacteria to be more readily "wetted," and when the bacteria are introduced into the body their union with the specific antibodies is enhanced. Larson did not regard the action of soap as involving a true chemical union, nor did he make note of any physical changes in the bacteria themselves.

Reasoner[8] has suggested that soap lather may be responsible for the rarity of the occurrence of extragenital lesions. He observed that when a suspension of *Treponema pallidum* was mixed with certain commercial soap solutions motility was inhibited at once, and the organisms became swollen, distorted, and reduced in number.

Spencer's[9] observations have shown that the density of suspensions of certain species of bacteria is reduced to zero by appropriate solutions of sodium ricinoleate, while the density of other suspensions is greatly increased. Apparently the reaction is an effect not dependent upon the surface tension nor upon the hydrogen ion concentration of the menstruum.

Clinical Study

In this report the results obtained in a study of 98 patients suffering from vaginal mycosis are presented. Before the institution of therapy an unlubricated speculum examination was made, and a moist-drop preparation was taken for microscopic confirmation of the diagnosis. In the questionable cases the vaginal contents were cultured on Sabouraud's agar medium, and the plates were read in 24 to 48 hours.

All patients were treated by a single method—namely, the vaginal instillation of the 3 per cent ricinoleic acid preparation. Approximately 5 c.c. of jelly were deposited deep into the vagina daily (on retiring) by means of a plastic syringe similar to those used in the instillation of contraceptive jelly. No douches or other medications of any kind were used during the course of this treatment. Abstinence from coitus was advised during the period of treatment.

All patients presenting symptoms or abnormal findings in the vaginal secretions were referred to a special clinic. The single constant complaint of patients with vaginal mycosis was pruritus. Other symptoms were burning about the introitus and rectum, dyspareunia, mild leucorrhea free of odor, and caseous-like material about the introitus and vagina. The pruritus varied from a mild to a severe unrelenting itch. The burning generally coincided with the degree of pruritus. Dyspareunia was present in the majority of the severe cases. The leucorrhea was predominantly scanty. The vaginal material is thick, white, or occasionally yellowish, caseous-like or "thrush" patches on the vaginal walls. The presence of this material is accompanied by a moderate to severe inflammation and edema of the vulva. Cervical erosions, cervicitis, polyps, and other common causes of leucorrhea were frequently found as incidental lesions.

Investigational Data

Table I shows the total number of patients treated with 3 per cent ricinoleic acid jelly. Of this number 68 were gravid, while 30 were nonpregnant women. On further investigation of the nonpregnant group it was found that 5, or 17 per cent, of these patients gave a history as well as clinical evidence of having

had vaginal mycosis in a recent pregnancy. As shown in Table I, 74 per cent of the pregnant group and 90 per cent of the nonpregnant group were considered cured. The failures occurred in 26 per cent of the pregnant group and in 10 per cent of the nonpregnant group.

An analysis of the nonpregnant failures discloses that all three patients used the 3 per cent ricinoleic acid jelly only sporadically. They would use it until relieved of their acute distress, then cease treatment. Consequently this group was intermittently troubled with vaginal symptoms. Even so, all of this group remained free of their symptoms when employing the material under study. Failures in the pregnant group totaled eighteen, with fourteen using the medication only sporadically. Hence only four were definite failures. The majority of this group were symptom free within 48 to 72 hours after the institution of the therapy. Symptoms recurred in one to four weeks if the patient was not cured at the time of interruption of therapy. All patients remained symptom free while on the medication. From the gravid group, four women used the medication irregularly until delivery.

TABLE I. VAGINAL MYCOSIS

TOTAL NUMBER STUDIED 98		CURED	FAILURES
Pregnant	68	50 (74%)	18 (26%)
Nonpregnant	30	27 (90%)	3 (10%)

It is shown in Table II that 36 per cent of the pregnant group and 26 per cent of the nonpregnant group became asymptomatic within 72 hours. Within one week 72 per cent of the pregnant group and 89 per cent of the nonpregnant group were asymptomatic.

The majority of cases were cured in two to eight weeks. Only a small percentage of the cases required nine or more weeks of therapy. Most cases will respond well within two to four weeks of therapy. A few cases were treated for longer periods during the early phases of this study to determine if there might be any tissue intolerance or untoward effect upon the pregnancy. Another small group of patients required longer periods of treatment because they used the 3 per cent ricinoleic acid jelly incorrectly.

In pregnancy the majority of the mycotic infections developed in the second trimester (Table IV).

The incidence of the infection in relation to the patient's age does not seem particularly significant especially as the age frequency for all pregnant patients in the Clinic has not been determined during this study but these data are presented in part of the protocol (Table V).

Comments

Ricinoleic acid 3 per cent in a buffered acid jelly vehicle is believed to be the medication of choice in the treatment of vaginal mycosis. It produces results superior to any method which has been tried in this clinic. (Propionate compound jelly has not been tried as our study was underway prior to its report.[11]) Ricinoleic acid in 3 per cent concentration in tragacanth-acacia jelly is a stainless, odorless, nonirritating, and efficient compound which is easily applied by means of a plastic syringe. The jelly's consistency at body temperature, adhesiveness, and wetting power permit it to come in intimate contact with the entire vaginal mucosa. In most instances it gives the patient complete relief from the intense pruritus within 72 hours and causes a disappearance of the causative organism in due time. This action should reduce the risk of oral

thrush in the newborn as a consequence of contamination during parturition.[10] Another important quality is the simplicity of its application. This reduces the number of office visits and furnishes adequate treatment, directed by the physician, through daily self-administration.

TABLE II. DURATION OF TREATMENT UNTIL ASYMPTOMATIC

TIME	PREGNANT			NONPREGNANT		
	NO.	PER CENT		NO.	PER CENT	
72 hours	18	36	72	7	26	89
1 week	18	36		17	63	
2 weeks	9	18		1	4	
3 weeks	4	8		2	7	
4+ weeks	1	2		0	0	

TABLE III. TOTAL LENGTH OF TREATMENT

DURATION	PREGNANT		NONPREGNANT	
	NO.	PER CENT	NO.	PER CENT
1 week	0	0	0	0
2 weeks	6	9	3	10
3 weeks	5	7	5	17
4 weeks	11	16	2	7
5 weeks	10	15	1	3
6 weeks	6	9	8	27
7 weeks	6	9	1	3
8 weeks	6	9	2	7
9-12 weeks	10	15	7	23
13-16 weeks	6	8	0	0
17+ weeks	2	3	1	3
	68		30	

TABLE IV. WEEKS OF GESTATION WHEN TREATMENT WAS INITIATED

TIME OF GESTATION	NUMBER OF CASES	PERCENTAGE
0-4 weeks	1	1
5-9 weeks	0	0
10-14 weeks	6	9
15-19 weeks	15	22
20-24 weeks	13	19
25-29 weeks	16	24
30-34 weeks	14	21
35-39 weeks	3	4
40 weeks	0	0
	68	

TABLE V. AGE INCIDENCE

AGE	PREGNANT		NONPREGNANT	
	NO.	PER CENT	NO.	PER CENT
15-19 years	4	6	0	0
20-24 years	26	38	2	7
25-29 years	18	26	4	13
30-34 years	16	24	13	43
35-39 years	4	6	8	27
40-44 years	0	0	2	7
45-49 years	0	0	1	3
	68		30	

The ricinoleic acid jelly has been used over prolonged periods without any ill effects. There has been no evidence of any sensitivity or intolerance to this preparation in this vehicle. Likewise, there have been no untoward accidents in the mothers or the newborn following its use. This therapy has been used until near term in a number of instances.

The criterion for cure is the absence of the clinical and symptomatic signs of vaginal mycosis together with the failure of recurrence of the infection after discontinuance of treatment. Cultures have been used in many, but the mere presence of a particular organism is not proof of an active infection.

The causative organism, *Monilia albicans,* is frequently found in the mouth, vagina, intestinal tract, and on the skin. These sites may easily serve as foci for reinfection, with the gastrointestinal tract being the principal offender. Active colonization of some portion of the intestinal tract has been demonstrated by Benham and Hopkins,[12] who have obtained positive cultures from this source for periods of over a year. The frequent scratching of the perirectal and perivulvar-cutaneous surfaces, faulty anal hygiene, and the contact of tight garments constitute excellent methods of reinoculation of the vulva.

Monilial infections involving other cutaneous areas in association with vaginal infections have been noted.[13] These are usually on the breasts of women, and more rarely on the penis of the conjugal partner. Such infections could and probably usually do result from the transference of fungus material from the vulva and vagina. In view of the fact that the incubation period of oral mycosis varies from 24 to 96 hours, and the vaginal incubation time should be comparable, some of our failures must be considered as reinfections.

One cannot stress too strongly the tremendous importance of strict personal hygiene; consequently prophylaxis is important.

Summary

1. A new and specific therapy for vaginal mycosis is described, namely, the use of ricinoleic acid 3 per cent in a buffered acid jelly.

2. This course of therapy in an uncorrected series produced 74 per cent of cures in the pregnant group and 90 per cent of cures in the nonpregnant group.

3. This method of therapy is characterized by prompt relief of the pruritus, disappearance of the causative organism, and prevention of spread of infection to other skin surfaces.

4. No ill effects or accidents have occurred over extended periods of treatment to either the mother or newborn.

5. Use of this preparation affords a convenient and most satisfactory method of self-treatment for the patient.

6. It is believed that the 3 per cent ricinoleic acid could be carried in suppositories or other suitable vehicles.

7. The skin, mouth, and intestinal tract serve as ready foci for reinfection of the vagina.

Correction

The summarization above *may or may not be* valid in assigning credit exclusively to ricinoleic acid as the specific fungicidal agent. The manufacturing pharmaceutist added oxyquinoline (0.1 per cent) as a preservative without approval and without informing either the authors or the medical director of Ortho Research Foundation. The fact that oxyquinoline was added came to light shortly before the galley proofs arrived.

Since oxyquinoline sulfate does possess some fungicidal action, an investigation was begun immediately to evaluate ricinoleic acid and oxyquinoline sulfate separately and in

combinations in a base jell. A report of these studies will be made. The combination of 3 per cent ricinoleic acid and 0.1 per cent oxyquinoline sulfate gave excellent results as indicated in the body of the paper.

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EVALUATION OF HORMONAL AND RADIATION THERAPY IN 190 CASES OF FUNCTIONAL STERILITY AND SECONDARY AMENORRHEA

Preliminary Report

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IT HAS been estimated that involuntary sterility occurs in about 17 per cent of all marriages.[1] Most clinicians agree that the male is at fault in about 40 per cent, the female in about 50 per cent, and both partners in about 10 per cent of infertile marriages.

In the female there are many conditions which contribute to sterility, especially, tubal and ovarian pathology, genital abnormalities, general systemic diseases, and nutritional deficiencies. The influence of nervous shock, anxiety, and mental diseases on infertility is also well known. During the first and second World Wars the effect of shock, strain, and anxiety on the physiology of the female pelvic organs has been thoroughly studied and its injurious effects demonstrated.[2]

Among other causes which frequently play an important role in sterility are: thyroid dysfunctions, pancreatic disturbances, particularly diabetes, and metabolic and endocrine disturbances.

This presentation, however, deals with endocrine disturbances of the pituitary-ovarian hypofunction type with clinical manifestations of sterility, secondary amenorrhea, and dysfunctional uterine bleeding, without any evidence of organic pathology. Such type of sterility is designated as "functional" or endocrine sterility.

Since secondary amenorrhea is associated with functional sterility in 94 to 96 per cent of cases,[3] and since these conditions for the most part have a common etiological basis, it is wise to consider them simultaneously.

It is the purpose of this paper to evaluate the relative merits of endocrine and radiation therapy in a series of 130 cases with functional sterility and 60 cases with secondary amenorrhea in women of a younger age group.

Diagnosis

The question arises as to how one arrives at a diagnosis of functional sterility. This diagnosis is made only after the status of the husband has been established and a thorough physical examination of the wife has ruled out systemic diseases, organic pelvic pathology, and mental and nervous diseases. The presence of tubal patency must be established by means of a Rubin test, salpingogram, or both. Basal metabolism, estimation of the specific dynamic action of the proteins, a Wassermann test, and a complete blood count are routine procedures in every case.

In addition, certain specific tests are necessary for the diagnosis of functional sterility. These tests consist of the following:

1. Endometrial biopsies
2. Vaginal smears
3. Basal temperature graphs
4. Estimation of the urinary gonadotropins

Endometrial biopsies usually reveal an abnormal pattern. Atrophic, proliferative, or hyperplastic endometrium is found when a secretory phase should be present premenstrually. In some patients, a secretory phase is found throughout the cycle and this, also, is abnormal, indicating a retained corpus luteum.

Vaginal smears and basal temperature graphs usually but not always parallel these abnormal endometrial findings.

The estimation of urinary gonadotropin is valuable inasmuch as an elevated gonadotropic titer indicates primary ovarian deficiency with compensatory pituitary overactivity. Absence of minimal amounts of urinary gonadotropin point toward pituitary insufficiency.

Methods of Treatment

After a thorough physical examination and completion of the laboratory investigations, as mentioned above, treatment is instituted and carried out according to a definite plan. Thyroid medication is given when indicated. Dietary adjustments are made, emphasizing the advisability of a high protein, low fat and carbohydrate diet in obese patients. In slim, hypotonic patients, a high caloric diet supplemented by vitamins and small daily doses of insulin is advised. If no results are obtained within a reasonable period of time, hormonal therapy is instituted. If there is still a lack of response within six to eight months, "small dose" radiation therapy is administered.

Many of the patients refuse radiation therapy and hormonal therapy is carried out for longer periods with intervals of rest. Another group of patients who never received hormonal therapy preferred the shorter, less expensive, and less tedious course of radiation therapy.

The criteria of success of either endocrine or radiation therapy consist of achieving pregnancy in sterility cases and of re-establishment of normal menstrual cycles in the unmarried women with secondary amenorrhea.

Endocrine Therapy

The endocrine therapy consisted chiefly of anterior pituitary or equine gonadotropins* supplemented by chorionic gonadotropins administered simultaneously or sequentially. Only adequate intensive therapy could be expected to be of any value; casual and irregular treatment is useless and succeeds only in discrediting the value of hormonal therapy. The equine gonadotropins are administered in doses of 200 to 500 international units for from 4 to 6 injections daily or every other day, in the first half of the cycle. Anterior pituitary gonadotropins are administered in a similar manner. Chorionic gonadotropins are administered in the second half of the cycle or combined with the anterior pituitary in the first half of the cycle.

*The equine gonadotropin was supplied by courtesy of Dr. W. H. Stoner of the Schering Corporation in the form of Anteron and of Dr. Murray Scott of Ayerst, McKenna and Harrison as Antex. Antex Leo was supplied by courtesy of Dr. Claire Folsome of the Ortho Research Foundation. Anterior pituitary gonadotropin, A. P. L., was supplied by courtesy of Dr. Murray Scott of Ayerst, McKenna and Harrison.

The variations in these techniques have been evolved by Hamblen,[4] Mazer,[5] Hall,[6] Rydberg,[7] Hawkinson,[8] and others. While we used several variations suggested, our best results were obtained with the Rydberg technique.

The possibility of forming antihormones must be remembered when large doses of either anterior pituitary or equine gonadotropins are used. According to Leatham and Rakoff,[9] equine gonadotropins develop specific antihormones after prolonged use of large doses. Nonspecific antihormones may be produced by anterior pituitary gonadotropins. In order to avoid this possibility which would negate the value of the therapy, these hormones should be used in large doses for short specified periods. The use of pituitary and equine gonadotropins should be alternated and a period of rest should be allowed after each series.

The above stimulative therapy will not achieve the desired results if the receptor organs (the uterus and the tubes) are hypoplastic. It is, therefore, necessary in such cases to produce growth and development by a pretreatment with sex steroids, such as estrogens and progestin. Results of endocrine therapy are analyzed in Tables I and II.

TABLE I. FUNCTIONAL STERILITY

1. Age	19 to 37 years		Average age, 27 years
2. Duration of Sterility	2 to 13 years		Average, 4½ years
3. Endocrine Therapy	76 cases		Conception 26 cases (34.2%) Miscarriages 4 cases
4. Radiation Therapy	54 cases		Conception 20 cases (35.2%) Miscarriages 2 cases
		37 endocrine resistent	Conception 12 cases (32.5%)
		17 radiation only	Conception 8 cases (47%)

TABLE II. 60 CASES OF SECONDARY AMENORRHEA IN UNMARRIED WOMEN

1. Age	16 to 29 years	Average age, 21 years
2. Interval between periods	4 months to 3 years	Average, 7 months
3. Endocrine therapy	32 cases	40.6% re-established periods
4. Radiation therapy	28 cases	46.4% re-established periods

Note: Of the 28 radiation therapy cases, 23 had previous endocrine therapy and 5 had no previous endocrine therapy.

Radiation Therapy

Irradiation of the pituitary and ovarian regions for the relief of "functional sterility" in the female is a universally accepted therapeutic procedure.

This therapeutic approach to the problem of sterility originated in Europe, when Halberstaedter,[10] established the selectivity of the x-rays for the ovary in 1905 and Beclere,[11] in 1926, reported the beneficial effects of roentgen irradiation of the pituitary in a case of secondary amenorrhea.

In this country, Rongy[12] and Rubin[13] were the first to apply this form of therapy in cases of functional sterility and secondary amenorrhea. In 1926, Rubin reported his first series of nine cases with a high percentage of successes; he later induced Kaplan, a radio-therapist, to extend this form of therapy to a large group of suitable cases with very encouraging results.

Several other clinicians and radiologists, Edeiken,[15] Mazer,[16] Finkler and Friedman,[17] Friedman and Finkler,[18] Hanman,[19] and Dripps,[20] applied this form of therapy and reported from 40 to 50 per cent successful results.

The original technique used by Kaplan was carried out by several clinicians with only slight variations in the dosage and number of treatments.

The greatest majority of our patients were treated by the modification of this technique as follows*:

Two hundred kilovolts therapy was employed with 0.6 mm. copper and 1 mm. aluminum filtration at 50 cm. target-skin distance. The half value layer was 1 mm. copper. The ovarian fields were 8 by 10 cm. and the pituitary fields 6 by 8 cm. A vaginal examination was performed in all married women and the exact location of each ovary was marked on the skin of the anterior and posterior pelvis. In unmarried women, the ovarian location was approximated by means of rectal examination. In most of the cases four treatments were given within a total interval of two weeks. The first treatment was delivered to the anterior right and left ovary, the second to the right lateral pituitary field, the third to the posterior right and left ovary and the fourth to the left lateral pituitary area. The skin doses were so calculated as to deliver a total of 80 r. into each ovary and into the pituitary gland. A few of the patients received similar therapy in weekly treatments over a period of three weeks. As far as possible the technique was kept constant for purposes of investigation.

It is understood that proper precautions must be taken before instituting radiation therapy. In secondary amenorrhea it is imperative to do a Friedman test before starting. In menstruating women therapy should be started immediately after the menses. Marital relations should be forbidden during the course of therapy. These precautions preclude the possibility of irradiating a women who may already have conceived. Results of radiation therapy are analyzed in Tables I, II, and III.

TABLE III. TIME INTERVAL BETWEEN RADIATION AND DIAGNOSIS OF PREGNANCY

Within 2 months	9 cases
Within 3 months	1 case
Within 4 months	2 cases
Within 6 months	2 cases
Within 7 months	3 cases
Within 10 months	2 cases
Within 1 year	1 case

Discussion

In our series of 76 patients treated with endocrine therapy, conception occurred in 26 patients or 34.2 per cent (Table I). Some clinicians report higher percentages of success. Winston,[21] reported conception in 44 per cent of cases, Hall,[6] in 55 per cent. Davis and Koff,[22] Siegler,[23] and Campbell and Sevringhaus[24] report favorable results with pituitary and equine gonadotropins. Rydberg[7] stated that the administration of equine and chorionic gonadotropins in suitable dosages almost always corrects secondary amenorrhea and functional sterility. Other workers, however, report poor results with equine and chorionic gonadotropins.[25, 26] Our results with endocrine therapy fall midway between the enthusiasm of the former workers and the pessimism of the latter. In view of a rather fair percentage of success which may be obtained with endocrine therapy I feel that patients should be given an adequate trial with hormonal therapy before radiation is attempted. Although there have been no untoward results on the offspring of the first generation of those treated with radiotherapy, possible genetic mutations in the third or fourth generation must be considered.

There is one point which is worthy of note in passing: Four patients who did not conceive re-established a normal endometrial pattern. Although this

*Great appreciation is extended to Drs. Milton Friedman and Carye-Belle Henle who treated the majority of our patients with radiation therapy. We also express our appreciation to Dr. Louis Levenson who treated some of the patients in this group.

indicates partial response to therapy it cannot be included in this group of successful cases.

Of the group who were treated by means of endocrines, four of the twenty-six conceptions resulted in abortion. This figure of about 15 per cent can be considered within the normal range of expectation.

In reference to secondary amenorrhea (Table II), our figures of re-establishment of menses in 40.6 per cent of cases are in agreement with those of many other workers. It is to be noted that the average age is 21 as compared to 27 years in those with functional sterility. It is, therefore, logical to assume that in the younger age group the end organs are more receptive to endocrine stimulation.

In reference to radiation therapy for functional sterility (Table I), twenty out of a total of fifty-four cases conceived (35.5 per cent). It must be noted that seventeen of the fifty-four cases had previously been treated with endocrine therapy and must be considered as endocrine resistant. Considering that these posed a more difficult problem from a therapeutic point of view, this percentage of success cannot be used as a true index of the value of radiation therapy. A more justifiable evaluation would be from a series of cases which had no previous endocrine therapy. Of 17 patients in this group, eight, or 47 per cent, conceived.

In the irradiated group, of the twenty patients that conceived, there were only two miscarriages (10 per cent), a figure which is well below the normal expectancy.

We were impressed with the rapidity of response to radiation therapy and analyzed the twenty women who conceived (see Table III). As seen from the table, nine patients conceived within two months and of this group four conceived within six weeks. The promptness with which conception followed the therapy demonstrated that the success is not a coincidence.

It is impossible to prepare such a table for endocrine therapy because this type of treatment is more prolonged and more difficult to evaluate.

Again, in secondary amenorrhea, as in functional sterility, radiation therapy has proved to be more successful in our 28 cases, 23 of which were endocrine resistant. In 46.4 per cent, normal menses were re-established.

Conclusions

1. One hundred thirty cases of functional sterility and sixty cases of secondary amenorrhea are reviewed for the purpose of evaluating the relative merits of hormonal and radiation therapy; one hundred eight cases were treated with endocrine therapy and eighty-two cases with radiation therapy.

2. In functional sterility, conception took place in 34.2 per cent of patients treated with hormones and 35.2 per cent treated with radiation.

3. In secondary amenorrhea, periods were re-established in 40.6 per cent of patients treated with hormonal therapy and 46.4 per cent of patients treated with radiation therapy.

4. Although radiation would appear to be ideal because of the high percentages of success, more rapid response and economy, great care must be exercised in the proper selection and study of cases considered for radiation therapy.

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35 Leslie Street

PREMATURE RUPTURE OF THE MEMBRANES*

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PREMATURE rupture of the membranes by definition is the rupture of the membranes at any time before the onset of labor.

The incidence of premature rupture is stated by recent authors of large series of cases to be higher than 10 per cent. This seemingly high incidence is due to strict adherence to the definition. In about 60 per cent of the cases of premature rupture of the mebranes the onset of labor is almost simultaneous with rupture; in a large portion of the remaining 40 per cent labor starts within several hours after rupture.

Material and Methods

A survey is presented of 102 patients with premature rupture of the membranes at the Cincinnati General Hospital over the period from January, 1936, to May, 1941. The total number of deliveries in these years was approximately 12,800. In reviewing the histories catalogued as premature rupture of the membranes, many had to be discarded because they were not instances of premature rupture of the membranes, but rather, rupture of the membranes early in labor. Obviously, the greater percentage of premature rupture of the membranes was not catalogued at all. Failure to catalogue premature rupture of the membranes appears to be a common offense. It seems especially easy to neglect to record this fact when the rupture of the membranes was followed shortly afterward by the onset of labor or when the patient had a favorable and uncomplicated course. Therefore, in this small series of cases there is a disproportionately high incidence of prolonged periods between rupture of the membranes and the onset of labor and a disproportionately large number of complications. This does not necessarily imply a correlation between length of time of rupture of the membranes and complications of labor and delivery, because in many patients with complications rupture of the membranes preceded the onset of labor by a short interval.

Data compiled from this series include: age, color, gravidity, parity, gestation period, length of time between rupture of the membranes and onset of labor, trauma or any other apparent cause for rupture of the membranes, toxemia, methods of induction of labor, duration of labor, presentation, methods of delivery, morbidity and complications, and infant mortality.

Results

Age.—Premature rupture of the membranes occurred most frequently in the age period from 20 to 25 years. There were no patients over 40 years of age in this series.

Color.—In this series the distribution according to color was equal.

Gravidity and Parity.—There were thirty-three patients in their first pregnancy and seven additional women who had not previously borne a viable

*Read before the Cincinnati Obstetrical Society, May 20, 1948.

infant. This is slightly higher than the general incidence of primigravidas and primiparas. There was also a slight increase in the incidence of premature rupture of the membranes among patients of high gravidity and high parity.

Gestation Period.—Forty-eight patients were at term, thirty-four in the eighth month, fifteen in the seventh month, and five in the fifth and sixth months of pregnancy.

Time Interval.—The length of time between rupture of the membranes and the onset of labor varied from less than one hour to fifty-six days. Rupture of the membranes occurred most frequently (thirty-three cases) between twenty-four hours and forty-eight hours before the onset of labor.

Cause.—In all instances, rupture of the membranes was spontaneous. There was no history of trauma or other apparent predisposing cause.

Toxemia.—There were only seven pre-eclamptic patients. This is lower than the average incidence.

Induction of Labor.—In 65 cases the onset of labor was spontaneous. There was induction with castor oil (in a few instances quinine was added) in thirty-one cases; there was induction by Pituitrin in one case, and there was bag induction in five cases.

Duration of Labor.—The average duration of labor showed no increase nor decrease from the average length of labor in cases without premature rupture of the membranes. However, the mode showed a shorter duration of labor. Cases in which the length of labor was increased were those in which abnormal presentations or disproportion was present.

Presentation.—In eighty-four cases there was vertex presentation; in sixteen cases, breech presentation, and in four cases, transverse presentation. There were two sets of twins in this series.

Prolapse of the cord occurred in seven cases. Prolapse of an arm occurred in three cases.

Type of Delivery.—The methods of delivery were as follows:

Spontaneous vertex	61
Elective low forceps	6
Operative forceps	10
Internal podalic version and extraction	
From vertex presentation	5
From transverse presentation	3
Dührssen's incision and operative forceps	1
Spontaneous breech	3
Breech aided	7
Breech extraction	6
Spontaneous evolution aided	1
Cesarean section	1

Uterine insertion of Braun bag was employed for cervical dilatation in eight cases.

Maternal Morbidity.—There were three cases of prepartum fever, twelve cases of intrapartum fever, and eighteen cases of postpartum morbidity. The longest period of hospitalization post partum of any case was eighteen days. One patient had pyelitis post partum. In one instance, a stitch abscess developed in the episiotomy wound.

In correlating fever or morbidity with the length of time between rupture of membranes and onset of labor, it was found that all three cases of prepartum fever occurred in the 24 to 96 hour period. Seven of the twelve patients with intrapartum fever were in the 24 to 72 hour group. Among the eighteen patients who had postpartum morbidity, ten were in the 1 to 12 hour period, five in the 12 to 72 hour period, three in the 72 to 240 hour period, and none in the period over 240 hours.

The period of this study in part antedated the employment of prophylactic chemotherapy, which is now routine.

Maternal Mortality.—There was one death in this series. The cause of death was lobar pneumonia, post partum, and the patient died on the eleventh postpartum day. Her membranes had ruptured 24 hours before onset of labor.

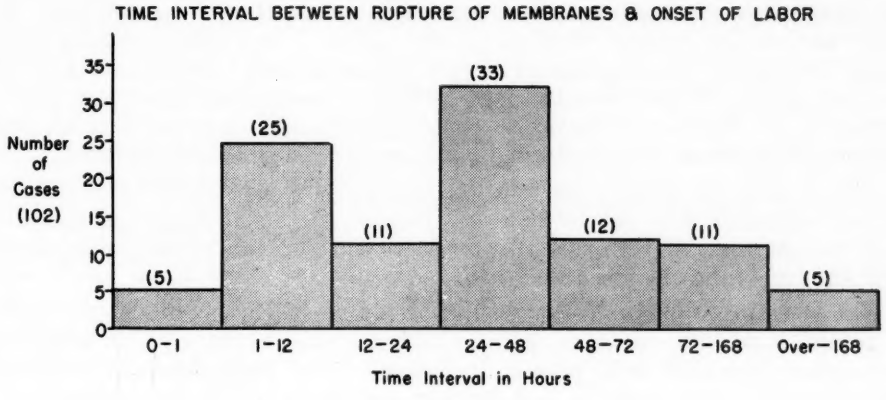

Fig. 1.

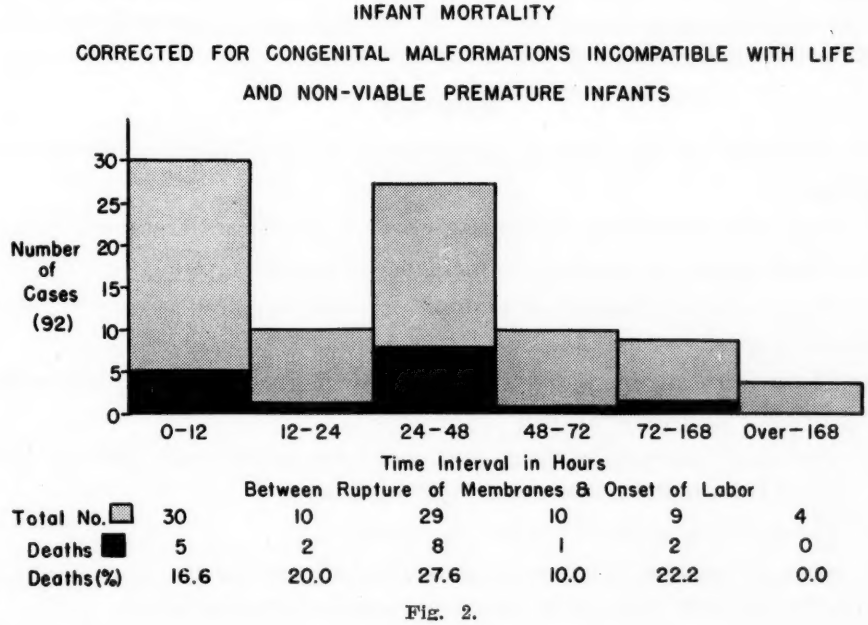

Fig. 2.

Infant Mortality.—The uncorrected infant mortality was 30 out of 104 infants, or 28.8 per cent. Making corrections for nonviable premature infants and for congenital malformations incompatible with life, the mortality was 18 out of 92 infants, or 19.6 per cent. There were 65 infants in the series whose birth weight was over 2,500 Gm. (5 pounds, 8 ounces), and 39 infants whose birth weight was 2,500 Gm. or less. Twelve of the infant deaths occurred in the former group. A breakdown of the infant mortality was made into the uncomplicated group and into the group composed of transverse presentation, prolapsed cord, and cephalopelvic disproportion. In the group of uncomplicated

vertex presentation there were 74 infants and only three deaths. All of these infants were stillborn. One had a mother with untreated syphilis, and his death occurred intrapartum. In the other two cases, the membranes had ruptured 41 and 66 hours, respectively, before the onset of labor. The birth weights were 5 pounds, 15 ounces and 6 pounds, 10 ounces, and both of the infants were macerated. Labor was not induced and it was of average duration. Delivery was spontaneous. The autopsies showed a subarachnoid hemorrhage in one infant and no conclusive findings in the other. Two infant deaths occurred among the eleven uncomplicated breech presentations. Both of these infants were premature. Labor was induced in one of these cases by Braun bag. The thirteen remaining infant deaths occurred with transverse presentations, cephalopelvic disproportion, and prolapsed cord on admission to the hospital.

There was no definite correlation between the corrected infant mortality and the length of time between the rupture of the membranes and the onset of labor, except that there was no increase in the mortality rate in instances in which the time interval was 48 hours or more.

An attempt to evaluate the results of interference was made by comparing the infant mortality in cases in which there was no attempt at induction of labor, cases in which there was induction of labor with castor oil or in a few cases castor oil with quinine, and cases in which there was bag induction. The infant mortality rate was the same with spontaneous onset of labor as with induction of labor by castor oil; it was higher in cases in which a uterine Braun bag was used for induction of labor. It was difficult to evaluate how effective castor oil was in hastening the onset of labor.

Summary

In this series of 102 cases of premature rupture of the membranes we have found that:

1. Age, color, gravidity, and parity were not significant factors.

2. There was no increase in the incidence of pre-eclampsia.

3. There was no history of trauma or other apparent cause for rupture of the membranes.

4. There was an increased incidence of malpresentations, cephalopelvic disproportion, and prolapsed cord.

5. The time interval between rupture of the membranes and the onset of labor ranged from less than one hour to fifty-six days.

6. The duration of labor was not increased.

7. Postpartum morbidity was not additionally prolonged when there was a long interval between rupture of the membranes and onset of labor.

8. The infant mortality was not increased with prolongation of the interval between rupture of the membranes and onset of labor.

9. The infant mortality rate was the same with spontaneous onset of labor as with induction of labor with castor oil. The infant mortality was higher when labor was induced by uterine insertion of Braun bag.

10. The total infant mortality was high, but in uncomplicated cases it was only slightly above average.

Conclusions

This survey shows that in cases of premature rupture of the membranes without other complications conservative treatment is indicated. The patient should be hospitalized, spontaneous onset of labor should be awaited or a medical induction with castor oil may be allowed, and there should be no interference with normal labor. Chemotherapy may be administered as a prophylactic measure.

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THE RELATIONSHIP BETWEEN THE HEMORRHAGIC BLOOD DYSCRASIAS AND HYPERMENORRHEA

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THAT the hemorrhagic blood dyscrasias may be associated with hypermenorrhea is recognized,[1, 2] and excessive menstrual flow may well be the presenting symptom in women whose final diagnosis is thrombocytopenic purpura.[3] The mechanism of this relationship remains uninvestigated, however, it having been generally assumed that uterine bleeding is controlled by the same mechanism by which rhexis in general is controlled.[4] Crossen and Crossen exemplify this assumption when they state that "uterine bleeding may be due to the condition of the blood without any local disease."[2] The opportunity during the past three years to see, in consultation, a considerable number of women with hematologic problems* has convinced the author of the incorrectness of this statement; and the present report suggests a possible mechanism by which the patient with hemorrhagic tendencies may acquire hypermenorrhea. The studies recorded are based on (a) menstrual blood loss measurements in patients whose clotting mechanism was artificially altered, (b) a survey of the histories of women suffering from hematologic disease with bleeding tendencies (thrombocytopenic purpura, aplastic anemia, etc.), and (c) a review of the pelvic findings, both gross and histologic, in a series of such patients.

A. *Blood Loss Measurements.*—Under normal circumstances menstrual blood has no clotting mechanism,[5] and would possibly be unaffected by alterations in the circulating blood coagulability. Furthermore, it has been demonstrated that the other physiologically nonclotting form of uterine blood, postpartum blood, is not increased in amount by hemorrhagic tendencies in the peripheral blood.[6] Accordingly, blood loss measurements, using the method previously described,[7] were carried out on each of six women through two consecutive menstrual periods.

With each patient one of the two periods was considered the control (the first in five of the cases, the second in one); during the other period the patient received anti-coagulant medications. In three of the subjects, dicumarol was started forty-eight hours prior to the expected onset of flow, and the prothrombin level held below 20 per cent for at least two days of the period. In the remaining three patients heparin was administered and the clotting time raised above twenty-five minutes for at least thirty-six hours of the period. In no patient was there a substantial increase of flow during the treated period, and averaging the groups, the blood loss for the treated and the control periods was approximately identical. There was, in other words, no immediate increase in amount of blood lost reflecting these particular alterations in clotting mechanism.

B. *The Histories.*—The records of 200 patients with hemorrhagic blood dyscrasias were reviewed. Of these, 61 were women within the menstrual years

*The author wishes to express his appreciation to the members of the Kinsman Hall Hematology Clinic for their cooperation in making patients available for this study.

(13 to 50). One patient had originally presented herself at the Gynecology Clinic with fibroids, and her record is not considered here. Of the remaining patients, twelve had or had had marked hypermenorrhea. Considered alone, these figures are not significant, since they must be compared to the average incidence of hypermenorrhea in the clinic population. As a control group, therefore, 60 consecutive women in the same age range who had registered in the Medical Out-patient Department were considered. Six of this group of patients had or had had a history of hypermenorrhea. These figures are summarized in Table I, and indicate that a history of hypermenorrhea is twice as frequent in the hemorrhagic blood dyscrasias as in the average clinic population.

TABLE I

	WOMEN IN MENSTRUAL AGE	NUMBER WITH HYPERMENORRHEA	PER CENT
Thrombocytopenic purpura	45	11	
Aplastic anemia	15	1	
	60	12	20
Medical Out-Patient Department	60	6	10

In reviewing these records, four cases were found in which ovarian irradiation or surgical castration had halted the excessive menstrual flow, although the hematologic picture remained unchanged, and the patient continued to manifest purpuric symptoms elsewhere. This would indicate that the excessive menses of the patient with hematologically caused bleeding tendencies may not be entirely analagous in its mechanism to the generalized purpuric manifestations.

Finally, one must be concerned about the 80 per cent of patients with hemorrhagic blood dyscrasias who did not display any alteration in their regular menstrual history. If the hypermenorrhea is explained simply on the grounds that the blood circulating through the uterus possesses a clotting defect, it would be reasonable to expect it to be, like the purpuric spots on the skin, an almost universal symptom. Some additional factor, other than the blood disease per se, must contribute the difference between those women who suffer excessive menstrual flow and those who do not.

C. *The Pelvic Status.*—Information as to the pelvic status of these patients was obtained from two sources: a review of postmortem material and an investigation of current cases.

Postmortems.—Material was available in the files of the Department of Pathology from 35 patients. These were women between the ages of 13 and 50 years in whom the history was adequate from the gynecologic point of view. In this particular group were included the leucemia patients as well as those with thrombocytopenia and aplastic anemia. Two of these patients had previously had hysterectomies, and of the remaining 33, ten had a history of a definite and substantial increase in menstrual flow. A review of the pathologic material in these 33 cases revealed the following pelvic entities:

Leucemic infiltration (myometrium or endometrium)	5
Fibroids	4
Endometrial polyps	2
Endometrial polyps and fibroids coexisting	1
Subendometrial hemorrhage	1
Tubal hemorrhage	1
Chocolate cysts of the ovary or ovaries	2
Follicular "cystic degeneration" of the ovaries	1
Endometrial hyperplasia	8

Actually there were more pelvic lesions than there were patients who had presented a history of menstrual abnormality, but the point of interest is that every patient with such a history had a pelvic lesion which could have been held accountable for her hypermenorrhea.

Current Cases.—Through the courtesy of Drs. Charles A. Doan and Bruce K. Wiseman, it has been possible for the past year and one-half to perform a dilatation and curettage at the time of splenectomy on all women in the menstrual years with thrombocytopenic purpura and associated hypermenorrhea. Combined with this, the pelvis has been explored manually from within the abdomen at surgery. Seven patients have been so examined and in an additional three cases it has been possible to obtain pathologic material from gynecologic operations performed elsewhere after the onset of symptomatology but prior to the patient's registration at this hospital. In the three patients operated upon elsewhere, chocolate cysts of the ovaries were encountered in one case, an old tuboovarian process in one, while in the third patient sections of the removed uterus revealed a marked hyperplasia of a nonsecretory endometrium in an otherwise normal-appearing organ. The findings in the seven patients seen in this hospital are recorded in Table II. Two of these patients (No. 2 and No. 3) are still under therapy for mild hypermenorrhea, the splenectomy having corrected the blood picture and purpuric tendency but not the excessive menses.

TABLE II

PATIENT	ENDOMETRIUM	UTERUS	TUBES	OVARIES
1	Swiss cheese hyperplasia	Large normal	Negative	Unilateral chocolate cyst
2	Interstitial hyperplasia	Normal	Old pelvic inflammatory disease	Multiple small unruptured follicles
3	Interstitial and glandular hyperplasia	Multiple fibroids	Negative	Negative
4	Interstitial hyperplasia	Large, congested	Old pelvic inflammatory disease? Old tubal hemorrhage?	Negative
5	Normal nonsecretory	Normal	Negative	Bilateral chocolate cysts
6	Swiss cheese hyperplasia	Normal	Active tubal bleeding bilateral	Tubovarian mass on left
7	Glandular hyperplasia	Normal	Negative	Normal size. Not visualized.

Discussion

To assume that alterations in the clotting mechanism of the circulating blood lead directly, without any local disease, to hypermenorrhea, commits one to the converse proposition that in a normal woman the duration and amount of menstrual flow is a function of the coagulability of the peripheral blood. In general, it has been felt that in normal women both the duration and the amount of menstrual flow have an endocrine control.

It is not the purpose of this paper to attempt to demonstrate in detail the etiologic relationship between the various pelvic findings encountered and hypermenorrhea. Admittedly, the morphologic findings in bleeding patients are often tenuous as etiologic explanations, and in cases of functional bleeding consist most often of hyperplasia of a nonsecretory endometrium which presumably reflects an endocrine imbalance. But it should be stressed that any one of the

patients examined in this group presented sufficient evidence to justify a diagnosis of bleeding on a strictly gynecologic basis, functional or organic, if the blood picture had not been known.

On considering the data cited above, therefore, it is suggested that: (1) a woman with hemorrhagic blood dyscrasia will not acquire hypermenorrhea without the intermediary of a local pelvic abnormality; (2) from the strictly gynecologic point of view this local finding would usually be considered sufficient to explain the bleeding organically, or to justify the diagnosis of functional bleeding of presumed endocrine cause; and (3) in most instances the local pelvic lesion itself results from the coagulation defect of the circulating blood (tubal hemorrhages, chocolate cysts of the ovary, etc.).

Essentially this would represent a reclassification of the factors to be considered in the etiology of hypermenorrhea. The hemorrhagic blood dyscrasias would not be classed as systemic causes, but as contributing to a local pelvic cause of excessive bleeding. From the immediate practical viewpoint, these tenets would re-emphasize the fact (forgotten in the patients surgically castrated prior to being seen in the Hematology Clinic) that the finding of tubal or ovarian masses in women with exaggerated menstrual flow may indicate the immediate, but not necessarily the entire etiology. Investigation of the hematololgic system remains imperative.

Conclusions

In a consideration of the relationship between excessive menstrual flow and blood dyscrasias with bleeding tendencies, it has been determined that:

1. Patients treated with dicumarol and heparin during a period showed no increase in amount of menstrual blood lost.

2. Those patients with hemorrhagic blood dyscrasias who also displayed hypermenorrhea presented sufficient evidence to justify a diagnosis of bleeding on a strictly gynecologic basis, functional or organic, irrespective of the blood picture.

In view of these findings a possible mechanism is suggested whereby the patient with hematologic bleeding tendencies acquires hypermenorrhea.

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HETEROSPECIFIC BLOOD GROUP PREGNANCY IN HEMOLYTIC DISEASE OF THE NEWBORN*

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REPORTS on isoimmunization during a heterospecific blood group pregnancy by the A and B agglutinogens are relatively rare in comparison with the vast number of publications dealing with the immunizing process by the RH factor.

A review of the literature emphasizes confusion which exists over many questions in relation to this problem. All authors now agree that congenital hemolytic disease of the newborn due to A-B sensitization usually takes a milder course with frequent spontaneous recovery than that due to RH-sensitization. However, severe or even fatal cases with liver damage and kernicterus also occur in cases in which the A and B agglutinogens are the basis of isoimmunization. Attempts have been made to arrive at a plausible explanation of some of its features. To analyze why isoimmunization with the A and B agglutinogens is so infrequent, the following factors have been suggested: lack of placental permeability to anti-A and anti-B; neutralization of these substances by water-soluble A and B Group substances present in the fetal plasma; lack of sensitivity of the fetal erythrocytes; and diminished activity of anti-A and anti-B at body temperature.[9]

Case reports on isoimmunization due to A-B sensitization are found in the American and English literature. Wiener[11] repeatedly mentioned its importance. The quality and quantity of an abnormal antibody, he believes, determine the varying clinical manifestations of erythroblastosis fetalis and, from this point of view, he, therefore, specifies three varieties of this disease; namely, icterus gravis, congenital hemolytic disease, and icterus praecox. The icterus praecox syndrome is commonly associated with A-B sensitization. According to Halbrecht,[6] icterus praecox is a milder form of pathologic icterus with minimal or no hemorrhagic manifestations. Wiener[10] explains the less severe character on several bases: the natural physiologic character of the a and b agglutinins in maternal sera which have in general little or no harmful effect on fetuses belonging to Groups A, B, and AB, the usually low titer of the agglutinins, and the fact that the natural isoagglutinins presumably are larger molecular aggregates which do not traverse the placenta easily.

Boorman, Dodd, et al.[3, 4] reported several cases. They felt that the amount of free A and B agglutinogen in the fetal plasma and body fluids plays a major role in the neutralization of maternal a and b agglutinins. Other investigators[2] could not find an appreciable amount of group specific substances in a number of cases. Tovey[9] believes that the placenta exerts a definite limiting effect upon the extent to which the maternal anti-A and anti-B agglutinins can enter the baby's circulation. Polayes[7, 8] reported a number of cases of isoimmunization by the A and B agglutinogen. Aubert[1] investigated one case with a remarkably high anti-A titer in a mother's serum.

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Case Reports*

CASE 1.—Mrs. A. F., 28 years old, white, four years married, a para i, gravida ii, with a history of death of her first child one year ago. Death occurred after twenty-four hours and a postmortem examination revealed a large interventricular septal defect of the heart.

She was now admitted on March 11, 1948, at 11 P.M. First labor pains began at 9 P.M. and at 2:55 A.M. of the following morning she delivered spontaneously a full-term male infant in right occipito anterior position. Her condition during labor was good. The placenta was expelled spontaneously. The cord appeared normal. The puerperium was uneventful and she was discharged on March 19, 1948, on her eighth postpartum day.

The infant appeared well developed and weighed 8 pounds at birth. However, his general condition was poor. Respiration was labored, the cry weak, and the airways appeared filled with mucus. The skin was of a pronounced pallid color and the face showed marked edema. The heart sounds were good and no murmurs could be heard. The abdomen presented no unusual signs. Liver and spleen could not be palpated. The question of a possible cerebral hemorrhage or a congenital heart lesion was raised by the pediatrician.

The laboratory findings were as follows: red blood cells 3,560,000, white blood cells 35,750, hemoglobin 80 per cent; differential count: polymorphonuclear leucocytes 41 per cent, stab forius 32 per cent, eosinophiles 2 per cent, basophiles 1 per cent, myelocytes 2 per cent, lymphocytes 16 per cent, monocytes 6 per cent; 86 nucleated red cells per 100 white blood cells.

A serological study of parent's and infant's blood revealed the following: mother: Group O, RH_1 hr'; father: Group A, rh HR'; baby: Group A RH_1 HR'.

It was evident that two incompatibilities were present; one between the main blood groups, the other in the HR-factor. No HR-antibodies could be detected in the maternal serum, either in saline or in albumin media. (Tests were performed in both AB-plasma and bovine albumin.) A series of 30 Group O rh-negative cells was used. However, the serum, when tested for anti-A and B agglutinins, revealed an abnormally high anti-A titer. This titer determined by several methods and rechecked repeatedly was found to be 1:200,000, while the reading of the anti-B was never higher than 1:200. Group A and group B cells with all available varieties of the RH-agglutinogen were tested under 22° and 37° Centigrade. Optimum agglutination was best obtained under room temperature (22° C.), while no pronounced deviation in titer could be detected between saline and albumin media. The infant's serum revealed the presence of maternal anti-A agglutinins up to dilutions 1:2 in saline and 1:8 in albumin media. Both maternal and infant's sera were tested 12 hours and 3 days post partum.

On the basis of these findings the diagnosis of erythroblastosis fetalis was made and the baby transfused immediately, by fontanel, with 60 c.c. of Group O RH-positive blood. The baby also received continuous oxygen, caffeine, and other symptomatic treatment.

The following day, on March 13, the red cell count rose to 4,690,000, the hemoglobin to 110 per cent; on March 14 and 15, the count declined to 3,890,000 (Hgb. 103 per cent), slight jaundice was noted, and the baby was transfused again. The following day, on March 16, the red cell count rose to 5,310,000 and the hemoglobin to 110 per cent, and remained at this level.

The further course was uneventful. On March 27, the baby showed the following blood picture: 5,300,000 red cells; hemoglobin 102 per cent; 9,800 white cells; polymorphonuclear leucocytes 39 per cent; stabs 5 per cent; lymphocytes 55 per cent; monocytes 1 per cent; and absence of nucleated red cells. Maternal anti-A agglutinins could no longer be detected. The baby was kept under observation until April 2, 1948, on which day he was discharged. At the present time the child is living and well.

CASE 2.—Mrs. R. L., 36 years old, white, para 0, gravida ii, had one spontaneous miscarriage at 18 weeks' gestation in 1947. During her second pregnancy she had the fol-

*We are grateful to Dr. David Gershenfield and Dr. L. E. Savel for the use of the clinical material.

lowing complaints: slight nausea and vomiting, occasional headaches, insomnia, and heartburn. She was admitted to Newark Beth Israel Hospital on May 27, 1948, at 11:55 A.M. First labor pains began at 3:45 A.M. of the same day. The membranes were ruptured artificially at 12:45 A.M. and at 2:49 P.M. she delivered a premature male infant. The delivery was performed by extraction of a breech presentation and forceps application on the aftercoming head. During labor her condition was good. The placenta was delivered spontaneously a short while after. The cord appeared normal. The course of the puerperium was uneventful and she was discharged on June 6, 1948, on her tenth postpartum day.

At birth, the baby weighed 6 pounds, 10 ounces and his general condition appeared good. No anomalies were noted. There was no clinical evidence of jaundice but the cord serum showed an icteric index of 28. On the third day of life the skin became icteric and the liver and spleen were readily palpable. However, the infant remained alert, had intact reflexes, and continued to take his formula well. The jaundice increased considerably during the following days and was still discernible at the date of discharge on June 6, 1948.

The hematological findings were as follows: On May 27, 1948 (immediately after birth): red blood cells 4,830,000, hemoglobin 118 per cent, white blood cells 36,600; differential count: polymorphonuclear leucocytes 43 per cent, stabs forius 6 per cent, eosinophiles 2 per cent, myelocytes 3 per cent, lymphocytes 28 per cent, monocytes 18 per cent, nucleated red cells not noted. On the following day there was no change in these findings (red blood cells 4,890,000; hemoglobin 112 per cent). On May 29, the red cell count dropped to 4,000,000 with a hemoglobin of 108 per cent and the baby was given 60 c.c. of Group O, Rh-positive blood by fontanel. On May 30, the red cell count was 3,800,000, the hemoglobin 104 per cent and another transfusion by the same route was administered. The next day (May 31) the red cell count rose to 4,730,000 and the hemoglobin to 112 per cent, and from then on the red cell count continued to climb slowly to 5,600,000 (June 5, 1948).

A serological study of parent's and infant's blood revealed: mother: Group O, RH_1 RH_2 HR'; father: Group A, RH_1 HR'; baby: Group A, RH_2 HR'.

The mother's serum had been tested for anti-A and anti-B agglutinins as follows:

January 14, 1948, 3rd month: anti-A 1:256, anti-B 1:8.

May 16, 1948, 8th month: anti-A 1:512, anti-B 1:8.

May 29, 1948, 2 days post partum: anti-A 1:1024, anti-B 1:8.

No maternal anti-A agglutinins could be detected in the infant's serum. The infant's serum was also tested for A and B group substances. For this purpose equal parts of infant's serum and maternal serum were mixed, incubated for 2 hours in a water bath at 37° C., and then titrated against A and B cells. At the same time the untreated maternal serum was titrated against the same cells. These tests yielded the following results:

Maternal serum: anti-A 1:1024, anti-B 1:8.

Infant's serum: anti-A none, anti-B none.

Maternal serum mixed with infant's serum: anti-A 1:256, anti-B 1:4.

Since the maternal serum was diluted with the infant's serum in a proportion of 1:2, the titer of the treated serum had to be multiplied by 2, so that the final reading was: anti-A 1:512, anti-B 1:8.

The inhibiting index of the infant's serum is computed by dividing the agglutination titer of the untreated serum by that of the treated serum:

$$\frac{1024}{512} = 2 \; \textit{Inhibition Index}^{3}$$

This experiment performed on the sera of Case 1 showed no inhibiting properties of the fetal serum whatsoever.

Discussion

From the serological point of view these two cases present a pronounced difference in titer between the a and b iso-hemagglutinins. An outstanding finding was the excessively high anti-A titer in Case 1 and the comparatively low anti-A titer in Case 2. Usually the newborn possesses at birth no agglutinins of

his own, and any agglutinins demonstrable in his serum are those of his mother which have filtered through the placenta. In Case 1 maternal a and b agglutinins penetrated the placental barrier and were readily demonstrated in the fetal serum in measurable quantities. Case 1 also presented an Hr-incompatibility without demonstrable Hr-anti-bodies, a factor which may have contributed to such an excessive rise of its anti-A titer.

A comparison of the anti-A titer of the two cases suggests the possibility that different fractions of the A agglutinogen may be responsible for such pronounced fluctuations in the serological findings. Braun and Schiff[5] found that the group specific substance "A" is a very complex one and consists of various protein and lipoid fractions, the latter being closely related to Forsman's antigen. That the group substance "A" plays an exclusive role in processes of isoimmunization, especially when it concerns mothers belonging to Group O, was shown by many workers in this field. Observations made on cases of Group "O" and "A" parents and Group "O" and "A" children revealed that the frequency of type A children is less in a mating with A fathers and O mothers than in cases of O fathers and A mothers; the infrequency of A children may be the result of loss by spontaneous abortion and stillbirth.

From the clinical and hematological viewpoint the first case presented a picture of erythroblastosis fetalis (congenital hemolytic disease). There was profound anemia with definite evidence of hemolysis and marked increase of nucleated red cells. At birth, the general condition of the baby was poor. Jaundice and some edema were present, but the liver and spleen were not palpable. Summarizing the findings of this case, it appears quite obvious that this infant's disease was due to isoimmunization of the mother by the blood factor "A" as demonstrated by the extremely high anti-A titer. The Hr-incompatibility may be regarded as of only minor importance because of the complete absence of any demonstrable Hr-antibodies.

The second case presented a picture similarly classified by Wiener[11] and described by Halbrecht[6] as icterus praecox. The infant showed an anemia with some evidence of hemolysis but no nucleated red cells. The jaundice appeared rather slowly and persisted for many days. The baby was well, nursed vigorously, was alert and had normal weight. Liver and spleen, however, were readily palpable.

Summary and Conclusion

1. Two cases of isoimmunization of Group O, Rh-positive mothers by the "A" agglutinogen are presented.

2. Enormous variations in the maternal titer may sometimes be encountered concerning the "A" agglutinogen.

3. The differences in anti-A titers in isoimmunization may be due to various fractions of the "A" agglutinogens.

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THE Rh FACTOR IN THE AMERICAN NEGRO

A Preliminary Report

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ONE is impressed by the abundant literature that has accumulated since 1939 on the subject of the Rh factor. Of particular interest is the racial incidence of the Rh factor and its relationship to the occurrence of erythroblastosis fetalis. The predominant amount of information available is in regard to the white population with national variations and a scant amount in reference to the Negro and Mongolian races.

Potter[1] has summarized most of the available material and cites the following figures: white population 85 per cent positive to the anti Rh_0 serum, Negro race 93 per cent positive, Mongoloid races, 95 to 99 per cent Rh_0 positive. Simmons et al.[2] in a study of 281 pure-blood aborigines found a 100 per cent Rh_0 positive reaction. Cole[3] in a recent study of 5,000 Rh determinations showed an over-all evidence of 86 per cent Rh_0 positive reactions. In his series 3.8 per cent (190 cases) were Negroes. Other reports on racial incidence from 1943 to 1946 have been tabulated by Potter.[4]

The occurrence at Provident Hospital of four confirmed cases of erythroblastosis fetalis within a period of eighteen months prompted us to study the prevalence of the Rh_0 factor in an all Negro obstetrical unit. The availability of material may be summarized thus: admissions to the unit with delivery for the years 1945 and 1946 were 2,607. The antenatal clinic attendance for the same period was 4,378.[5]

Methods of Study

1. Patients attending the antenatal clinic were typed at random for the Rh_0 factor and as far as possible the patient's husband was also typed.
2. Requests were made that all private patients admitted to the obstetrical service be typed for the Rh factor.
3. Individual physicians were encouraged to have Rh_0 factor determinations done as a routine procedure in their antenatal care. These reports were submitted at the time of admission to prevent duplication.
4. At the time of blood typing on other hospital services Rh_0 factor determinations were requested.
5. All cord bloods of Rh-negative mothers and those babies having any of the six cardinal signs of the erythroblastosis syndrome[6] were typed.

In order to increase the validity of our study and through the suggestion of Dr. Potter[7] three test procedures were employed: (1) commercial animal serum, (2) human serum using the slide method, and (3) human serum using the test-tube method. In the first procedure the test was performed in two steps: one, the preparation of the blood suspension by carefully cleansing the finger, pricking it with a fine bistoury, and dropping two full drops of blood into 0.5 c.c. of a buffered normal saline solution containing 1 per cent sodium citrate; second, the placing of one drop of the cell suspension on a clear glass slide at 70° F., placing next to this one drop of commercial anti-Rh_0 serum.

The two were carefully mixed and the slide set aside for three minutes. At the end of this time the mixture was observed until a six-minute period had ended. Care was taken to prevent too vigorous agitation and breaking of the clumps which makes a positive test appear negative. All of the slides were read with oblique lighting against a white background. In the positive test clumping was always clearly visible in six minutes, at which time all observations were terminated. The slide method using human sera (glutinin test) was performed by placing two drops of oxalated blood on a clean slide at 70° F. One drop of the Anti Rh_0 serum was added and the mixture spread over the slide. The slide was placed over a viewing box and rotated back and forth. Clumping was designated as Rh_0 positive. The test was terminated in two minutes. The test tube method was done by mixing one drop of Anti Rh_0 serum with a drop of 2 per cent fresh blood suspension in a small narrow test tube. This was incubated at 37° C. for one hour and the reaction read grossly by inspecting the sediment in each tube. The tube was rotated at an angle in order to separate the sediment from the bottom of the tube. The tubes were allowed to stand one hour at room temperature and then read macroscopically.

Results

A total of 1,000 Rh_0 factor determinations were done at random. In this series 150 (15 per cent) were Rh_0 negative. In the male group, 94 (81.0 per cent) were Rh_0 positive and 22 (19.0 per cent) were Rh_0 negative. In the female group, 756 (85.5 per cent) were Rh_0 positive and 128 (14.5 per cent) were Rh_0 negative (Table I). In regard to the procedures used there is noted to be no apparent statistical differences between methods (Table II). Of the 128 Rh_0 negative female patients, 86 were obstetrical patients who had delivered. In this group there were eight who had babies or stillbirths with one or more of the signs of the erythroblastosis syndrome. The occurrence of the erythroblastosis factor in this series is 9.3 per cent.

TABLE I. DISTRIBUTION RH FACTOR IN AMERICAN NEGRO (CHICAGO)

		REACTION TO ANTI RH SERUM*			
		POSITIVE		NEGATIVE	
SEX	NUMBER TESTED	NUMBER	PER CENT	NUMBER	PER CENT
Males	116	94	81.0	22	19.0
Females	884	756	85.5	128	14.5
	1000	850	85.0	150	15.0

*$X^2 = 13.7$.
$P = .001$.

TABLE II. COMPARISON OF ANTI RH SERUM TEST METHODS*

		REACTION			
		POSITIVE		NEGATIVE	
METHOD	NUMBER TESTED	NO.	PER CENT	NO.	PER CENT
I Commercial serum (animal)	622	532	85.5	90	14.5
II Slide (glutinin test) (human serum)	259	221	85.5	38	14.5
III Test tube (human serum)	119	102	85.8	17	14.2
Total	1000	855	85.5	145	14.5

*I and II $X^2 = 1.5$ $P = 0.22$ $n = 1$.
I and III $X^2 = 1.6$ $P = 0.20$ $n = 1$.
The short formula for Chi Square in Fourfold Tables was used.[14]
P value is from Fisher cited by Yule and Kendall.[15]

There can be no definite statement made as to the correlation of the blood groupings and the presence or absence of the Rh_0 factor. The high incidence of the O type blood is in keeping with the distribution of O typed blood in the general Negro population. The remaining blood types are of normal distribution. It is interesting to note the correlation of the blood types with the data of Wiener[8] on tests of 500 Negroes (Table IV). With this specific correlation there may be justification in postulating that the incidence of Rh_0 factor is lower in the American Negro seen in the semi-private clinics of the Chicago area than in areas previously studied.

TABLE III. TESTS WITH ANTI Rh_0 SERUM ON THE AMERICAN NEGRO

INVESTIGATORS	NO. TESTED	PERCENT RH-POSITIVE	PERCENT RH-NEGATIVE
Landsteiner and Wiener[11]	113	92.0	8.0
Levine[12]	264	95.5	4.5
Tisdale and Garland[13]	283	91.2	8.8
Authors	1000	85.5	14.5

TABLE IV. RH FACTOR DISTRIBUTION WITH BLOOD TYPE (PER CENT)*

NO. TESTED	RH FACTOR	O	A	B	AB
743	Present	59.2	22.8	13.2	4.8
115	Absent	33.3	36.3	27.7	2.4
500†	——	47.0	28.0	20.0	5.0

*International Classification.
†Wiener.

Discussion

As mentioned by Potter,[4] many of the studies on racial incidence have been carried out with only one type of serum and have distinguished only the presence or absence of antigens reacting with Anti-Rh_0 serum. In our series we used only the Anti-Rh_0 serum and no attempt was made to determine the existence of the various varieties of Rh antigens. In the investigation of racial origins Boyd[9] mentions that if data are to be reliable the character studied should not be modified by environment and should be nonadaptive and that it should be obtained by means sufficiently objective to permit exact duplication by any investigator. Potter[4] quotes Boyd in that, "The fundamental units of racial variability are populations and genes, not the complexes of characters which connote in the popular mind a racial distinction. Much confusion of thought would be avoided if all biologists recognized this fact. The geography of genes, not the average phenotypes, must be studied. Only a few attempts to apply this method in practice have been made to date. The most successful one among them is that concerning the blood groups in Man." These statements are well applied in this study in the determination of the Rh_0 factor in such a heterogeneous population as the urban northern Negro. A factor for the differential incidence in the phenotype Negro may be due to a genotypic variance characteristic of that group; this is probably due to the effects of geographic location, racial intermixture, and possibly mutations during the period of migration. In our series the use of the Bernstein formula[10] for racial admixture does not apply.

The importance of this study is in the consideration of transfusions and intragroups transfusion reactions and the noting that Rh_0 factor determinations should be done as a routine procedure.

During the course of our study, communication[17] with Freedmen's Hospital, Washington, D. C., reported a higher incidence of the Rh_0 factor than

in our present series. No available data to date have been received on the occurrence of erythroblastosis in their series.

Since the initiation of this study we have done approximately 2,700 additional Rh_0 determinations. In this data, as in the previous data, there was the same range with the standard deviation being less than ±1.5. These analyses will be reported in a future paper.

Summary

1. One thousand Negroes were tested at random for the Rh_0 factor. In this series 15.0 per cent were Rh_0 negative, a figure that corresponds with that of the Caucasian population.

2. Three test procedures were employed and one statistical variation was noted.

3. The blood groupings were noted to be of the normal distribution found in the general Negro population.

4. The incidence of the erythroblastosis factors in this series was 9.3 per cent.

5. A brief discussion of racial characteristics is included and a comment made on routine Rh_0 factor typing.

The authors wish to acknowledge the technical assistance of Mr. Walter L. Turner and Mr. Randolph Hughes.

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THE ROLE OF THE FETAL BACK IN ATYPICAL OCCIPUT POSTERIOR POSITIONS*

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IT HAS long been recognized that posterior and transverse positions of the occiput at the onset and during labor do not represent deviations from normal and should not by necessity be viewed with concern.

Failure of rotation of these initial positions caused by either faults of the maternal pelvis, soft parts, or labor result in persistent posterior or transverse positions which may spell more difficulty for the mother, the obstetrician, or both. The difficulties thus experienced have been variously ascribed to the larger cephalic diameter necessary for passage, the lack of flexion, and the inefficient direction of drive. In addition, it is often highly significant that the very faults in the maternal pelvis which contribute to the persistence of these positions are frequently etiologically significant in their manifest difficulties.

To these should be added another factor which deserves further elaboration: that is, namely, the fetal back. The importance of this was fully recognized by Pomeroy many years ago in describing his technique of manual rotation. In the following two cases, attempt will be made to demonstrate that the position of the fetal back may be of considerable significance in persistent occiput posterior positions and that its position should be used as a guide as to the direction of operative rotation.

CASE 1.—T. K., a 25-year-old primigravida whose expected date of confinement was Jan. 29, 1942, was admitted to the hospital on February 20, roughly three weeks overdue. Early labor pains were irregular and mild so that actual labor did not start until the following day. The patient had a rather uneventful first stage of thirteen hours' duration. There was noted, however, the existence of a posterior position, presumably a left occiput posterior judging by palpation of the fontanels. On abdominal examination the bulk of the baby seemed to be on the maternal right as with marked dextrorotation and the small parts were anterior and to the left.

After a prolonged second stage the patient was taken to the delivery room where the scalp was just perceptible at the vulva and the peak of a well-molded head with a large caput was on the pelvic floor. On vaginal examination at this time, the biparietal diameter was well through the pelvic inlet and the head was arrested in midpelvis in a left occipitotransverse position. Due to the presence of moulding and caput this was checked by palpation of the fetal ears and brow. A cephalic application with the Kielland forceps was made by wandering the anterior blade into position rather than in the classical manner. Traction was applied in the transverse position in order to bring the head to a lower level for rotation. This was met with considerable resistance and rotation anteriorly could not be accomplished at either above or below the level of arrest.

The forceps were then removed and the accuracy of the previously diagnosed position was rechecked and found to be correct. Suprafundal pressure was then applied and it was observed that with pressure the occiput tended to rotate toward the hollow of the sacrum

*Read before the New England Obstetrical and Gynecological Society, May 5, 1948.

so that it took up a left occiput posterior position. From that position the occiput was rotated manually to the hollow of the sacrum. A cephalic application was then made with the Kielland forceps to the direct occiput posterior position and with no difficulty at all the posterior occiput was rotated 180 degrees through the maternal right side to an occiput anterior position. The forceps were then replaced by an axis traction forceps and after moderately strong traction with added fundal pressure an 8 pounds 4 ounce infant was delivered. The child cried spontaneously and was in fair condition. There were no vaginal lacerations other than the mediolateral episiotomy which had been done in the perineal phase. The infant had a transient unilateral facial weakness, otherwise was normal. Both mother and baby were discharged on their ninth postpartum day after an uneventful hospital course.

In this case (Fig. 1) the back was clinically posterior and to the right whereas the occiput was to the left; this required rotation first to the hollow of the sacrum and then anteriorly through the maternal right or opposite side.

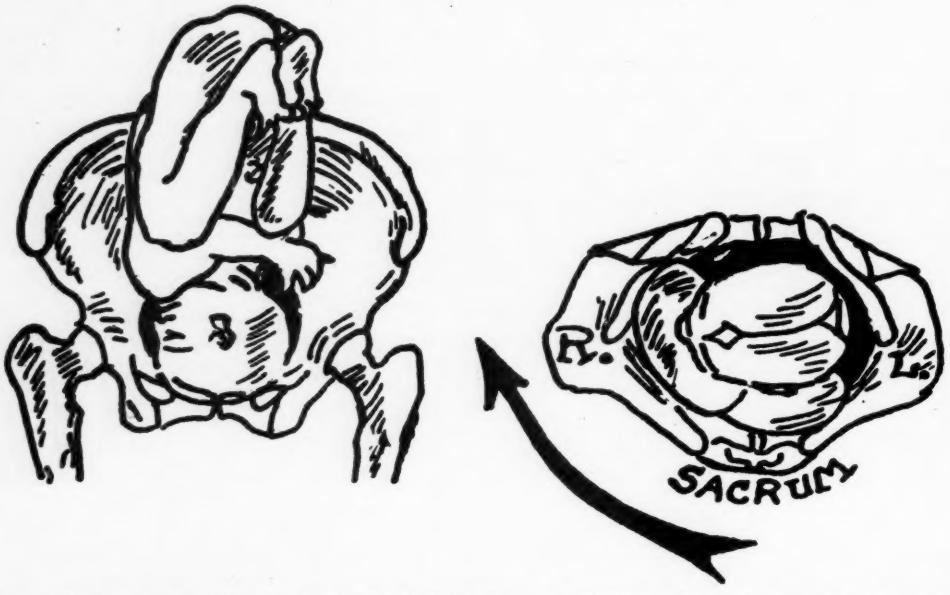

Fig. 1.—Vertex presenting in left occipitotransverse position, fetal back occupying the right posterior oblique. Arrow shows direction of successful rotation toward the fetal back.

CASE 2.—L. G., a 22-year-old gravida ii, para i, with a previously normal labor history and a normal antepartum course, was admitted to the hospital on March 19, 1948. Her expected date was March 15.

The patient experienced a mild desultory first stage of fourteen hours' duration. After a one-hour second stage the patient was examined in the delivery room and the diagnosis of a persistent right occiput posterior position in low midpelvis was made. Thickness of the abdominal wall was such as to make identification of the small parts impossible. The fetal heart was on the right side.

A cephalic application was made to the right occipitoposterior position with the Kielland forceps. With adequate available anterior-posterior space, attempt was made to dislodge the head upward to effect rotation at a higher level. This attempt was met with sufficient resistance to warrant its abandonment. Attempt to rotate at the level of arrest to a right occipitoanterior was also met with considerable resistance. The forceps were then removed and the previously diagnosed position was checked and found to be correct. The forceps were then reapplied as before and the occiput rotated to the hollow of the sacrum. In this position traction was applied in an attempt to deliver it as a direct occiput posterior. Here again moderately strong traction failed to advance the head. After consideration,

an attempt was made to rotate the head from its present direct posterior position through 180-degree arc on the left side of the maternal pelvis. With great ease and with no undue force this was accomplished and the occiput brought anteriorly to the symphysis. An 8 pound, 2 ounce infant in good condition was then delivered through the outlet without difficulty following a mediolateral episiotomy. Restitution occurred 135 degrees to the left side to the left occiput posterior position. There were no vaginal lacerations. Both mother and infant were discharged from the hospital on their sixth postpartum day in good condition after an uneventful hospital course.

In this case (Fig. 2) the direction of finally successful rotation plus the direction of restitution leaves little doubt that the back occupied the left posterior oblique position while the occiput occupied the right posterior oblique position. This required rotation first to the hollow of the sacrum and then anteriorly through the maternal left or opposite side.

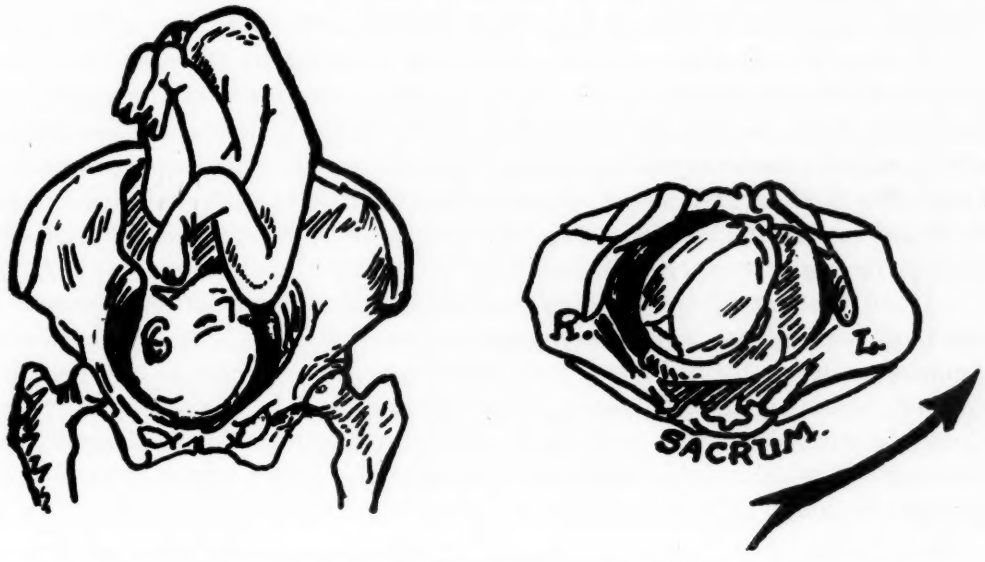

Fig. 2.—Vertex presenting in right occipitoposterior position, fetal back occupying the left posterior oblique. Arrow shows direction of successful rotation toward the fetal back.

Discussion

These two cases represent situations in which, by virtue of torsion of the infant's neck, the occiput and the fetal back were on opposite sides of the maternal pelvis. It is felt that this condition is not as uncommon as experience would lead one to believe and that it may be the cause of some cases of failure of rotation which have often been handled by internal podalic version or other means.

The possible mechanism of this torsion is rather difficult to understand. It seems logical to suppose that probably at the onset of labor the occiput and fetal back were in alignment. During labor, as is not uncommonly the case, the occiput probably rotated to the hollow of the sacrum. With further progress of labor changes in flexion may have occurred which brought the occiput to a more dependent position and thus started its anterior rotation but in the opposite direction. This line of reasoning can be considered only speculative in character.

From the study of these two cases and on consideration of purely mechanical principles, it would seem evident that the fetal body and back exert a very decided effect not only on success but also on the direction of rotation of the occiput. A frequent observation in spontaneous deliveries is to see the occiput restitute after delivery 135 degrees to the oblique posterior position. We must assume then that the back had failed to rotate with and accompanying the head. Thus we know that the occiput can and does frequently rotate 135 degrees on the back without cervical or brachial injury. In spite of this, an external attempt to rotate the anterior shoulder to accompany the rotation of the occiput is mechanically sound. Due to the anatomy of the cervical spine and the brachial plexus attempts to rotate the occiput on the back beyond 135 degrees may result in irreparable damage to the fetus.

In view of this it is of utmost importance to recognize the position of the fetal back before embarking upon any operative rotation. This is especially important when the occiput is directly posterior in the hollow of the sacrum, in which case the back may occupy either the right or left oblique posterior position. The fetal heart is not a reliable indicator since in such positions it may be heard on either side depending on whether it is transmitted through the back or through the anterior chest.

If on account of thickness of the abdominal wall or for other reasons the fetal back cannot be definitely outlined, palpation of the fetal head while fundal pressure is being exerted from above may give the clue as to the direction of rotation. If these measures should fail, and in any event, rotation should be carried out with such gentleness as to detect an abnormal resistance encountered which might indicate a torsion of the infant's neck beyond safe anatomical limits.

Summary

1. Two cases of occiput posterior positions are reported in which the occiput occupied the opposed side of the maternal pelvis from the fetal back.

2. Successful rotation in each case described an arc greater than 180 degrees toward the side of the fetal back.

3. The importance of recognizing the position of the fetal back before embarking upon operative rotation is emphasized.

The author acknowledges with appreciation the preparation of the accompanying illustrations by Dr. Gilbert Heublein.

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CARCINOMA IN SITU OF THE UTERINE CERVIX*

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IN 1932, Dr. A. C. Broders[1] gave the term "carcinoma in situ" to a type of epithelial lesion, clinically not malignant, sometimes found by the microscopist in removed tissue. Broders' term is clearly descriptive. The same lesion has been designated as "intraepithelial cancer," "pseudomalignancy," "precancerous lesion," "epithelial restlessness," and "covert cancer."

Broders said of "carcinoma in situ" that it is a condition in which malignant epithelial cells and their progeny are found in or near the positions occupied by their ancestors. The carcinomatous cells have not penetrated the so-called basement membrane. In this condition, moreover, the cells which have undergone malignant change have not migrated. If such migration had taken place, it would be manifested by the cells having entered the connective tissue interstices or any part of the blood or lymph vascular system.

The superficial malignant change which is the subject of this article occurs at, or distally adjacent to, the area where the squamous and columnar epithelium meet at the external uterine orifice. It is, then, adjacent to the secreting columnar cells of the endocervix. In this region, the alkaline intrauterine secretions probably are in their greatest concentration. It is here, furthermore, that the alkaline intrauterine secretions are first subjected to the acidifying and liquefying action of the vaginal fluid.

The lesion seems to involve primarily the squamous, protecting or covering epithelium. It may be so tiny as to be entirely removed by an ordinary nasal punch when this instrument is used to remove a specimen for biopsy or it may extend laterally over the portio vaginalis to involve an adjacent portion of the vaginal wall.

Various pathologists have found, in this early lesion, abnormalities in size of cells, abnormalities in size and staining qualities of the cell nuclei and a jumbled arrangement of cells. However, the cells do not seem to have possessed the property of invasiveness. The aberrations listed suggest loss of strength or softening of the extracellular framework. The foregoing phenomena stimulate speculation as to the process which caused this distortion and these cellular changes. Did some intracellular force cause the framework to give way; did some extracellular disruptive substance fail to be inhibited? Was the morphologic cellular change due to intracellular or extracellular alteration? At all events, an abnormal and seemingly uncontrolled growth is a predominant characteristic of cancerous tissue.

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Literature

Borst-Würzburg[2] is credited with describing, in 1904, a lesion of the type under discussion, which affected the skin. Schiller[3] gave credit to Schottländer and Kermauner who reported, in 1912, observations of conditions of the uterine cervix similar to those described, and Schiller[4] himself, in 1936, reported a study of serial sections of all cervices brought to the laboratory where he worked. He felt that stages in the process of formation of cancer of the uterine cervix could be identified, the first and earliest stage being that known as the "carcinomatous zone" stage, wherein invasion or penetration of the so-called basement membrane had not occurred. This superficial lesion could spread within the surface epithelium to various degrees. In more advanced stages there would be some localized invasiveness and in a third stage the process would be further extended.

Such investigators as TeLinde,[5, 6] Novak,[7] Martzloff,[8] MacFarlane,[9] and their associates, and more recently Meigs[10] and Ayre[11] have published conjectures as to causation of processes of this type. These early lesions might be considered to be smoldering cancers which potentially are destructive.

Survey of Cases and Results of Follow-Up Investigation

I wish to report a survey of thirty-two cases of early lesions of the sort here under consideration, encountered at the Mayo Clinic from 1932 to 1946, inclusive (Table I).

TABLE I. PARTIAL SUMMARY OF CASES

Material	Year of diagnosis	1932	1936	1940	1941	1942	1943	1944	1945	1946	TOTAL
	Number of patients	1	1	2	5	2	4	6	6	5	32
	Age of patients, inclusive years	20-29		30-39		40-49		50-59	60-69		
	Number of patients	5		8		12		6	1		32
Relevant symptoms, history, and signs					Present			Absent			
	Chief complaint relative to pelvis, patients				18			14			32
	History of bleeding, patients				12			20			32
	Previous pregnancy, patients				27			5			32
	Pelvic treatment previous to year of diagnosis, patients				8			24			32
	Cervical lesion	Erosion	Polyps	Leuco-plakia		Cystic change		Normal	Not record-ed		
	Patients, number	16	7	2		4		1	2		32
Diagnosis	Biopsy	In office, plus cauterization		In office, biopsy only				In operating room			
	Patients, number	14		4				14			32
	Squamous-cell epithelioma grade	1		2		3		4			
	Patients, number	1		4		24		3			32
Definitive treatment	Type of treatment	Abdominal hysterectomy		Vaginal hysterectomy		Dilatation curettage and radiation		None at clinic			
	Patients, number	19		9		3		1			32

In May, 1947, a survey of the records to include 1946 was made, and the findings were deduced from the records of a recent physical examination or

from a questionnaire. The interval between May, 1947, and the date of definitive treatment varied widely. In nine cases the interval was one year; in six cases, two years; in six cases again, three years; in two cases, four years; in five cases, five years; in one case, seven years; and in another case, fifteen years. Two patients had died of heart disease but in no case had carcinoma recurred.

In Table I it is recorded that in fourteen cases a specimen for biopsy was removed in the office and cauterization was performed. In eight of these cases carcinoma was not found later in the surgically removed cervix. In Table I, also, the notation appears that a specimen for biopsy was obtained in the operating room in fourteen cases. In four of these, no carcinoma was found in the remaining tissue which was removed at hysterectomy. Of these four cases, conization had been performed previously in two, in one at the clinic and in one elsewhere; the removed specimen was forwarded to the clinic for examination by a pathologist. In one of the four cases, a Sturmdorf operation previously had been performed elsewhere; again the removed specimen was submitted and the diagnosis confirmed at the clinic. In the remaining case of the four, the surgeon at the clinic evidently had included all of the carcinoma in the portion he removed for biopsy.

Comment

In the five years, 1940 to 1944, inclusive, 739 cases of carcinoma of the cervix were encountered at the clinic, including nineteen cases of carcinoma in situ, an incidence of 2.57 per cent of all cases of cervical carcinoma encountered in the five years. In this same five years, as an office procedure, approximately 1,600 cervical specimens were taken for biopsy, in eleven of which carcinoma in situ was found, an incidence of 0.68 per cent. The period of five years was taken for this part of the study because over-all figures for incidence of cervical carcinoma were available for that period.

In the entire period of fifteen years, during which the thirty-two cases of this series were collected, in eighteen the diagnosis was based on tissue removed for biopsy as an office procedure. Of these eighteen cases, in fourteen the cervix was cauterized, also as an office procedure. When these fourteen patients subsequently underwent total hysterectomy, the cervices of eight were free of carcinoma, whereas some carcinomatous tissue remained in the cervices of the other six. The remaining four patients of the eighteen were not subjected to cervical cauterization in the office. Of these, three underwent total hysterectomy and carcinomatous tissue was found in the removed cervices. The remaining patient of the four refused to undergo hysterectomy and she has not been heard from since.

All consultants of the Department of Obstetrics and Gynecology contributed to the foregoing statistics. All, furthermore, concur in finding nothing diagnostic of carcinoma in the clinical appearance of cervices in cases such as are considered herein. The importance of this article, finally, is that it points out how valuable and perhaps lifesaving an act it may be for the gynecologist to take a specimen for biopsy from any cervix of abnormal appearance, even if that appearance does not suggest to him the presence of carcinoma.

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NAUSEA AND VOMITING INDUCED BY PREGNANCY OR BY ADMINISTRATION OF SYNTHETIC ESTROGENS; TREATMENT WITH ANTIHISTAMINIC COMPOUNDS

A Further Study of an Additional 50 Cases

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IN PREVIOUSLY published research, the author has recorded considerable proof that the nausea and vomiting of early pregnancy are due to an allergic reaction of the patient to the secretion of her own gravid corpus luteum.[1] He has also shown that the nausea and vomiting which occur following the administration of diethylstilbestrol are an allergy and are similar to, if not identical with, the nausea and vomiting of pregnancy, occurring in the same individuals who have had nausea and vomiting of pregnancy and in the same degree.[2]

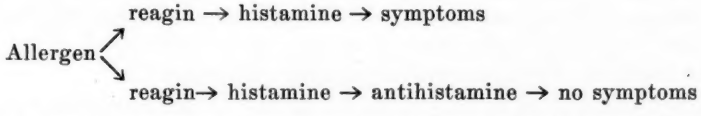

Fig. 1.—Schematic representation of mode of action of antihistaminic compounds.

Since the mechanism of allergic reactions is commonly accepted to be that of allergen + reagen → histamine release from body cells, and since one of the actions of histamine in producing allergic symptoms is to produce spasm of smooth muscle which is part of a nausea and vomiting complex, it was decided to treat a series of cases of nausea and vomiting of pregnancy with some of the antihistaminic compounds.

Material

To date (June 19, 1948), twenty-nine cases of nausea and vomiting of pregnancy have been treated using Benadryl (beta-dimethylaminoethylbenzhydryl ether hydrochloride) in eighteen cases, and Histadyl (thenylpyramine hydrochloride) in eleven cases. Twenty-seven cases were completely relieved. One case was improved and one case was unimproved.

Of the group, three cases were classified as plus 4 (pernicious vomiting). All three of this series were tertigravidas, one aged 24 years, one 29, and one 32. One woman, about eight weeks' gestation, had been vomiting almost all ingested food and fluid for two weeks and when first seen was in a severe state of starvation, acidosis, and avitaminosis. Intravenous Benadryl in doses of 50 mg. every three hours did not alter her course any appreciable amount, although she was given, in addition, intravenous glucose and saline solution, pyridoxine hydrochloride, thiamine, and adequate sedation. She continued to vomit until she aborted five days later. The other two patients, each at about six weeks' gestation, had been nauseated eight or ten days and vomiting incessantly for two days. They stopped vomiting within twenty-four hours with 50 mg. Benadryl intravenously every four hours and were then maintained symptom free with 100 mg. orally four times a day.

After five days this dosage was reduced to 50 mg. orally three times daily until they were well into the fourth month of pregnancy, when it was discontinued. They are still progressing normally, now in the sixth month of pregnancy.

Eight cases were classified as plus 3 (nauseated all day long and vomiting three or four times daily). These patients were given 50 mg. intravenous Benadryl four times the first day, which stopped the vomiting in each case, and then 100 mg. Benadryl or Histadyl orally three times a day until all nausea ceased at which time they were instructed to reduce the dose gradually as their symptoms permitted. Most of them were able to reduce the dosage to 50 mg. twice daily within a ten-day period and keep symptom free on that small dosage, leaving it off entirely by the time they entered their second trimester.

Twelve cases, at about six or seven weeks' gestation, were classified as plus 2 (nauseated all day long and vomiting from none to two times daily). These patients were given Benadryl or Histadyl in 50 mg. doses three times a day and told to double the dose if they needed it. Eleven were totally relieved within three days. The other patient was partially relieved but an increase in the dose caused dizziness and drowsiness of which she complained more than the nausea. She was tried on both drugs but the side effects were the same. She was given 100 mg. pyridoxine hydrochloride intravenously three times a week for two weeks following which time she was placed on 50 mg. Histadyl at bedtime and after three weeks of this therapy, having been maintained symptom free save for occasional morning nausea, the drug was discontinued.

Six cases, of four to seven weeks' gestation, were classified as plus 1 (severe morning nausea without vomiting). All six of these patients were totally relieved within twenty-four hours by 50 mg. Histadyl or Benadryl morning and night and after a week were able to reduce the dosage to 50 mg. at bedtime for another week and then were told to take it only as their symptoms indicated. Five were able to discontinue the drug entirely and the sixth patient found the 50 mg. at bedtime necessary for relief.

Of this entire series, nine were gravida iii, all having had nausea and vomiting with previous pregnancies; nine were gravida ii, six of whom had had nausea with their previous pregnancy and two of whom had not. Ten were primigravidas and one was a quintigravida who had had nausea and vomiting with her last two pregnancies. Ages ranged from 19 to 37 years. With the exception of the one who aborted, all are still pregnant and progressing normally, most of them near term.

Nausea Induced by Diethylstilbestrol or by Hexestrol Relieved by Antihistaminic Compounds

Since it had been shown that the nausea and vomiting caused by the synthetic estrogens, especially diethylstilbestrol, are also an allergy,[2] it was believed that the antihistaminic compounds should here also prevent nausea and vomiting by acting as a histamine antagonist, the mode of action being most likely that of showing a greater affinity for histamine than does the cell receptor mechanism.

Eleven patients, known to have severe vomiting after the ingestion or injection of ordinary doses of diethylstilbestrol and ten patients known to be allergic to hexestrol were given antihistaminic compounds with each dose of estrogenic drug and in each case a full therapeutic dose of the estrogen was tolerated with no side effects.

One patient, a nullipara, aged 29 years, who has been under my observation for several years because of severe metrorrhagia is of particular interest. This woman is very allergic to progesterone, developing large bullous hives following its administration. She has a plus 4 skin reaction to intradermally injected natural corpus luteum extractions. Both diethylstilbestrol and hexestrol in ordinary doses cause severe nausea and vomiting, although these two drugs in large doses, apparently by dilating the spiral arterioles of the endometrium, check her severe hemorrhaging promptly. They have been used repeatedly, during the past several years, to save frequent necessity of curettage, even though the nausea they induce is most severe.

Upon the last hospital admission this patient was bleeding severely. Ten mg. diethylstilbestrol were given parenterally and repeated in three hours. With the first dose, 100 mg. Benadryl were given orally and repeated at four-hour intervals. Menstruation checked markedly within a few hours and the patient was then given 18 mg. hexestrol and 300 mg. Benadryl daily (orally) for the following three days by which time bleeding had ceased. During the entire time from admission to cessation of flow the patient experienced absolutely no nausea or vomiting, much to her surprise, for she was not advised of any change in medication from that given during previous hemorrhagic periods.

Seven days before her next menstruation was due this patient was given 10 mg. progesterone in oil and 150 mg. Benadryl daily for five days. Two days later she had a normal type menstruation but had no hives for the first time in many trials endeavoring to control her hemorrhages with progesterone.

Six other patients in this series, with the menopausal syndrome, all multiparas, varying in age from 42 to 49 years, all having experienced severe nausea and vomiting with pregnancies and all having had previous nausea from diethylstilbestrol, were given 1 mg. diethylstilbestrol and 150 mg. antihistaminic compound (three cases treated with Benadryl and three with Histadyl) daily. Each patient was relieved of her varied menopausal symptoms and none of the six had any nausea from the estrogen.

Four other patients, aged 17 to 19 years, each a virgin with severe dysmenorrhea, were given 2 mg. stilbestrol and 150 mg. Benadryl daily to suppress ovulation and thus obtain a painless anovulatory menstruation. This had been tried previously but the nausea from the estrogenic drug was so intense it had to be withdrawn. With the addition of the antihistaminic there was no nausea experienced and each patient was given a painless withdrawal-type bleeding for three consecutive months while this treatment was being employed.

Patients Allergic to Hexestrol

Another series of ten patients, who had been previously unable to take hexestrol because of nausea gave the following results:

One woman, aged 26 years, had had severe nausea with her one pregnancy seven years before. She was given 6 mg. hexestrol daily for secondary amenorrhea but was severely nauseated by it. She volunteered to take hexestrol with Histadyl experimentally to see if it would prevent the nausea. She was given 200 mg. Histadyl daily and was able to take as much as 18 mg. hexestrol daily without any nausea. After this experimental dosage, the dose was reduced to 3 mg. twice daily which she was able to take without any side effects as long as she continued 50 mg. Histadyl twice daily.

Five nulliparas, aged 19 to 24 years, who had previously been unable to take hexestrol for treatment of their dysmenorrhea, were all able to tolerate 18 mg. daily without nausea as long as they were given 150 to 200 mg. antihistaminic compound (three cases treated with Histadyl and three with Benadryl).

Four women, ages 45 to 49 years, all with previous nausea and vomiting from pregnancy and from hexestrol, were able to tolerate 3 mg. of this drug daily, which was adequate for relief from their menopausal symptoms, as long as they were given 50 mg. of either Histadyl or Benadryl with the hexestrol.

Comment

Results using Benadryl or Histadyl were equally good, several patients being given both drugs at different times. A few patients complained slightly more of drowsiness or dizziness from Benadryl when it was first started but within two or three days they developed a tolerance to it. To prevent any side effects from the antihistaminics, I now start the patient with 50 mg. of the drug at bedtime, then have her increase the dose by 50 mg. each day until her symptoms are relieved. In this way the dosage is kept to a minimum and the side-effects are almost totally prevented.

Although we have not as yet been able to identify the hormone which acts as an allergen in producing the nausea and vomiting of pregnancy and/or the nausea and vomiting induced by the synthetic estrogens, I feel that this report with the facts published in previous reports is adequate proof that the symptom-complex is an allergic reaction.

With the use of antihistaminic compounds to prevent the allergic reaction, adequate, inexpensive, and prompt relief can be accorded almost all of these patients.

It might be of interest here to state that in the search for the unknown hormone which acts as an allergen several factors have been eliminated. It has been shown, in a previous publication, that progesterone is not the guilty hormone. Since that report a series of skin tests upon nauseated individuals, properly controlled, using a solution of pure relaxin, showed no correlation between the intradermal reactions and the patient's symptoms. A similar series was done using a preparation of sheep whole pituitary with like negative results. It is my opinion that the allergen will eventually be shown to be either the luteinizing hormone of the pituitary or an as yet unidentified secretion of the corpus luteum, or some metabolic by-product of one of these hormones.

Summary

1. Twenty-nine cases of nausea and vomiting of pregnancy have been treated with antihistaminic compounds with twenty-seven cases cured, one improved, and one unimproved.

2. Eleven patients with various diagnoses, unable to take diethylstilbestrol because of nausea and vomiting induced by the drug, were given antihistaminic compounds in addition and all could tolerate the full therapeutic dose of the estrogen with no nausea or vomiting.

3. Ten patients unable to take hexestrol because of nausea and vomiting were able to take the full dose without nausea when antihistaminic drugs were added.

Conclusions

1. The nausea and vomiting of pregnancy are allergic reactions to an unidentified hormone, probably from the gravid corpus luteum.

2. The nausea and vomiting induced by diethylstilbestrol and hexestrol are allergic reactions.

3. Antihistaminic compounds such as Benadryl or Histadyl can completely cure or prevent the nausea and vomiting induced by pregnancy or by the synthetic estrogens.

I wish to express my appreciation for generous quantities of Benadryl capsules and injectable Benadryl supplied by Parke, Davis & Co., Detroit, and Histadyl capsules supplied by Eli Lilly & Co., Indianapolis.

I wish also to thank Dr. Frederick L. Hisaw, Harvard University, for a quantity of relaxin prepared for intradermal tests. The extraction of sheep whole pituitary gland, for which I am most grateful, was furnished through the courtesy of Dr. A. A. Hellbaum, University of Oklahoma School of Medicine, and Dr. W. H. McShan, University of Wisconsin.

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Oklahoman Building

CONTROL OF STILBESTROL VOMITING

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USE of diethylstilbestrol has been hampered by the side effect of nausea and vomiting. Other estrogenic drugs are satisfactory in treatment of the menopause, but in therapy of the functional ovarian disorders in younger women stilbestrol (as it is commonly called) remains valuable. It is economical in the large doses required and apparently more beneficial than some of the other drugs.

The author has had excellent results in treating menorrhagia, pelvic pain, and cystic ovaries with 5 mg. doses of stilbestrol. A survey of 107 such cases was published in 1945. A second series of 86 cases was published recently.[5] In the first series,[1] 50 per cent had some nausea and 9.3 per cent had to stop the drug because of vomiting.

Due to the similarity of this nausea and vomiting to that seen in pregnancy, it was decided to use the drug which has been so successful in treating the vomiting of pregnancy.[2, 3, 4] A single dose of 50 to 100 mg. of pyridoxine was given intravenously to all patients who complained of severe nausea or of vomiting after starting the twenty-day oral course of 5 mg. stilbestrol daily. Twenty of the 86 patients requested pyridoxine. This is higher than the 9.3 per cent of the control series who could not take the drug, but some of these twenty patients could have continued to take the drug despite their discomfort, had pyridoxine been withheld. Three, or 3.5 per cent, of the 86 continued to vomit after the pyridoxine when they resumed taking the stilbestrol. This compares with the 9.3 per cent of the control series who discontinued stilbestrol because of vomiting.

As a second control group, 18 pregnant women to whom vomiting was quite troublesome were given 50 to 100 mg. pyridoxine intravenously. Fourteen obtained relief and four were unrelieved. This is very similar to the treatment of the stilbestrol induced vomiting cases described above where seventeen were relieved and three were not.

In summary it appears that the use of 100 mg. pyridoxine intravenously will reduce by two-thirds the number of patients who are unable to take stilbestrol because of vomiting.

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THE EFFECT OF DIETHYLSTILBESTROL IN THE PROLONGATION OF PREGNANCY

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IT HAS been observed[1, 2] that patients treated with stilbestrol for low estrogen effect alone usually went beyond term if stilbestrol was not stopped at least three weeks before the expected date. It was thought that this observation might be checked by other investigators, and the following observations are presented.

Procedure

Since stilbestrol is now being used for threatened and habitual abortion, premature labor, and some other accidents of pregnancy,[3, 4, 5] thirty-five consecutive pregnant patients, among whom were nineteen threatened abortion cases and three habitual abortion cases, were given large and unphysiologic doses of "des" stilbestrol* from the first time they were seen, all during pregnancy and during labor. This was done in order to note whether the administration of stilbestrol would prolong pregnancy. It has been suggested that stilbestrol may cause the fetus in missed abortions to be retained. Two cases diagnosed as threatened abortions turned out to be missed abortions while stilbestrol was being given.

Table I gives the total number of milligrams, the number of days that stilbestrol was taken, the average daily dose, amount taken within twenty-four hours, up to and during labor, and the calculated days of pregnancy when the patient delivered.

Summary

Thirty-five patients were given varying amounts of stilbestrol during pregnancy. The average age of these patients was 26 years, the youngest 13 and the oldest was 39.

These patients had an average of 33,320.5 mg. total dose and a daily average of 244 mg.

These patients were taking an average of 499 mg. of stilbestrol every twenty-four hours at the time of the onset of labor.

They delivered on an average on the two hundred sixty-eighth day of pregnancy, so estrogenic withdrawal at term may not be an important factor in the cause of labor. The fetuses in missed abortions were not retained, but appeared to be expelled when stilbestrol was given.

Conclusions

It might fairly be concluded that stilbestrol, even in large and unphysiologic doses, did not prolong pregnancy in this series nor in missed abortion cases.

*"des" diethylstilbestrol, Grant Chemical Company.

TABLE I. SUMMARY OF 35 PREGNANT WOMEN RECEIVING "DES" STILBESTROL

NAME	TOTAL MG.	NO. DAYS TAKEN	AVERAGE DAILY DOSE	AMOUNT TAKEN IN THE 24 HOURS BEFORE AND DURING LABOR	DAY OF PREGNANCY DELIVERED
G. W. H.	66,565	155	429.45	500	240
W-19 E. B.	7,300	18	405.05	500	271
W-24 V. W.	33,000	68	485.29	600	289
W-29 C. R. N.	30,525	175	172.46	400	275
W-24 V. E. S.	9,100	31	293.5	300	266
W-28 L. N. P.	14,026	216	64.96	200	254
W-33 R. W. D.	2,750	58	36.36	375	302
W-36 S. E. W.	25,350	78	325	275	292
W-26 R. R. R.	28,200	201	140.30	125	278
W-39 A. W.	14,650	168	87.34	250	245
W-28 L. P.	22,400	150	149.33	600	270
W-29 C. A. R.	11,300	52	213.46	300	248
W-25 M. W.	112,925	134	824.79	100	280
C-30 J. J. A	71,385	249	206.02	400	292
W-25 N. G. F.	120,730	185	652.34	1500	223
W-34 L. M. L.	25,350	260	97.5	300	299
W-31 E. M. L.	22,475	85	264.4	200	263
W-26 F. J. F.	6,500	70	92.85	200	257
W-24 D. A. C.	5,650	143	38.81	25	207
W-18 H. M. H.	84,807	213	298.15	2000	256
W-35 E. E. C.	27,027	82	329.57	875	280
W-13 E. N. H.	69,025	182	379.20	1000	292
W-34 A. E. E.	50,825	208	244.93	100	281
W-26 J. E. P.	30,505.5	104	293.32	25	268
W-24 J. P.	9,650	193	50	50	302
W-25 L. M. S.	33,464	874	87.14	25	312
W-25 M. E. T.	10,500	58	181.03	50	266
W-22 W. D. D.	33,750	195	173.07	100	243
W-22 W. W. F.	36,635	77	475.78	2200	278
W-37 S. E. D.	42,215.75	165	255.85	750	266
W-21					

TABLE I—CONT'D

NAME	TOTAL MG.	NO. DAYS TAKEN	AVERAGE DAILY DOSE	AMOUNT TAKEN IN THE 24 HOURS BEFORE AND DURING LABOR	DAY OF PREGNANCY DELIVERED
R. B. D. W-26	46,400	228	291.23	50	270
J. B. B. W-31	22,225	136	163	700	266
E. M. C. W-24	11,150	201	55.47	400	298
E. W. G. W-26	30,050	138	217.75	150	277
F. D. W-24	12,400	190	65.26	100	725

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AN AID TO THE REMOVAL OF THE GELLHORN PESSARY

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THE Gellhorn pessary has proved to be a very useful instrument in the treatment of prolapse of the uterus, especially in cases in which operative treatment is inadvisable. However, removal of the pessary may not be accomplished with as great ease as is its insertion; in many instances its removal may be exceedingly difficult. This difficulty is due to the inability of the operator, no matter how skillful he may be, to retain a grasp upon the small end of the pessary. A simple device has proved successful in overcoming this difficulty. A small hole is bored through the ball tip at the small end of the pessary. The teeth of a tenaculum can then be inserted at each end of the hole and a firm grasp on the pessary obtained (Fig. 1). The pessary can then be removed smoothly and easily. The tenaculum also serves as an aid in guiding the pessary during removal. The hole can be drilled in any standard Gellhorn pessary whether it be made of hard rubber or of the newer plastic materials. The openings should be smoothed to prevent irritation to the vaginal mucosa. Cleaning is easily accomplished since the hole extends through the pessary from one side to the other.

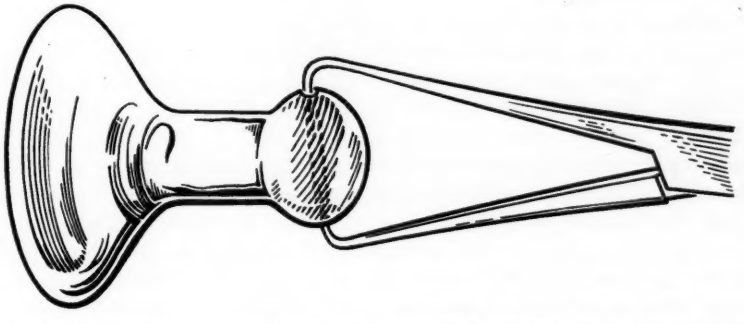

Fig. 1.—Gellhorn pessary grasped by teeth of tenaculum through hole in small end.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology

The Disorders of Menstruation and Treatment[1] by Colombo is a faultlessly, even luxuriously presented monograph in two parts. The ovario-pituitary relationship is considered from the experimental aspect, with extensive protocols fully illustrated, dealing mainly with castrated white rats and the effect of various attempts at replacement therapy. Many illustrations on the morphology of the pituitary resulting from these experiments are given. However, the screen is too coarse, so that interpretation of these reproductions is really impossible. In a series of noncastrated rats, as little as 275 International Units of estrogen caused marked hypophyseal changes with ovarian luteinization while, in the castrate, 4,200 International Units caused only partial restoration. No effect was produced by 1 mg. of progesterone. These experiments show nothing particularly new and gave rise to no conclusions.

The second portion is purely clinical, detailing the various general conditions which can influence the menses, taking up sterility, anovular menstruation, amenorrhea, menorrhagia and metrorrhagia, etc. Estrogenic therapy is considered but Karnaky's results evidently escaped the author's attention. R. T. FRANK.

Surgical Techniques by the Vaginal Route[2] by Eric Weber is a monograph which shows that it is written by a well-trained gynecological operator who knows the value and limitations of the vaginal route from A to Z. The book covers the entire subject. The methods for relieving cystocele and prolapse are antiquated. The description of the extended vaginal hysterectomy for carcinoma is good. The illustrations, no matter from what point of view regarded, do not come up to even the lowest standards. They are not only inartistic but in the majority of cases inadequate. R. T. FRANK.

This large monograph by Pierre Durel[3] deals solely with the inflammations of the cervix, from anatomical, clinical, and therapeutic aspect. In the second edition he has the collaboration of Dutheil and Autrand. The first part deals with the histology and the clinical symptoms. The great majority of the illustrations are not up to the standards required in this country. The authors are justly against prolonged attempts at cauterization if the slightest doubt as to the possibility of malignancy exists. In diagnosis, syphilis may prove a stumbling block. They discuss cervicitis due to trichomonas. Considerable space is devoted to the laboratory bacteriology and serology for gonococcus. The therapeutic situation has been entirely altered since the first edition in which sulfonamide therapy was the main standby before the advent of penicillin. Endocrine aspects of the situation are discussed although, in my opinion, these do not apply to strictly cervical

[1] **Los Desordenes de la Menstruacion y su Tratamiento. Base experimental de la interrelación prehipófiso-ovárica.** By Emilio Colombo, 327 pages. Editor "El Ateneo," Buenos Aires, 1949.

[2] **Techniques Chirurgicales Vaginales. Possibilitiés et Limites.** By Eric Weber, Strasbourg. Préface du Professeur A. Labhardt. 144 pages. J. B. Baillière et fils, Paris, 6e, 1948.

[3] **Les Métrites du Col. Etude Anatomo-Clinique Nouveaux Traitementes.** By Pierre Durel, Médecin de l'Hôpital Saint-Lazare. Avec la collaboration de Lucien Dutheil, Ancien interne de l'Hôpital Saint-Lazare et Hubert Autrand, Ingénieur I.E.N. Deuxième Édition Revue et Augmentée. 333 Pages. Masson et Cie, Éditeurs, Paris, 6, 1948.

situations. Chapters are devoted to general medical, to chemical and thermal cauterization, high frequency currents, diathermia, coagulation, and even hysterectomy in certain instances. The concluding chapter deals with metritis and prostitution particularly as it applies to the transmission of gonorrhea. The therapy of cervical conditions has been so much affected by our improvements in therapy that much simplification of this type of monograph may be expected in the future. It is a pity that the cancer situation has not been considered more fully in the monograph. R. T. FRANK.

Another monograph by Usandizaga,[4] which appeared in 1946, has come into our hands. It is a second edition, the first one having appeared in 1941, forming a part of Practical Medical Manuals issued by the same publishers, a long list of which has appeared in the past. There are excellent descriptions and microscopic illustrations of erosion, its healing, and epithelial metaplasia. There are good colored macroscopic illustrations of the conditions of the cervix, their etiology and diagnosis. Especially diagnoses excluding cancer are taken up. Local therapy including cautery, coagulation, and operation are described; the sulfonamide drugs are discussed. Evidently penicillin and exfolliative cytology were not ready to be incorporated. This is an excellent, well-illustrated monograph which will have to be brought up to date soon again. R. T. FRANK.

Obstetrics

This **Treatise on Obstetric Labor,**[5] by Richard Torpin, may be regarded as expressing his personal opinions to a large degree and details the clinical obstetric practice in the hospital of the University of Georgia. The author's attitude regarding surgical obstetrical procedures is markedly conservative. He has found that employment of fluids, dextrose, transfusions, oxygen, sedation, and rest are far more favorable for the mother and fetus in many emergencies than immediate, however skillful, surgery. On his service version and extraction, except for transverse presentation, Dührssen's incisions of the cervix, and use of dilating bags have become obsolete, while postpartum packing of the fundus is necessary in approximately 1 per cent of deliveries. The ability of the uterus to expel its contents may be determined in labor by a few simple clinical tests as to the interval, length, and height of contractions, so that abnormalities, other than disproportion, may be quickly recognized and properly treated.

He has divided the material into forty-one chapters and appends a considerable list of pertinent case histories. The erythroblastosis and Rh-factor sections have been contributed by Edith L. Potter and Philip Levine. For amnesia-analgesia he prefers the intravenous use of pentobarbital sodium and scopolamine, with local anesthesia of the perineum by 1 per cent procaine solution for episiotomy.

He offers an interesting solution for rural obstetrics in suggesting and describing a delivery-room setup as a part of a rural physician's office or county health center. The patient, after such office delivery, is sent home within a few hours or the next day to convalesce in her home.

Torpin's service has seen a case of eclampsia on an average of every eighteen days over a period of ten years. The treatment of the eclamptic patient consists in the use of intravenous magnesium sulphate, the control of convulsions by pentobarbital sodium, adequate nourishment and attention to the water balance, oxygen, and, when the condition improves or becomes satisfactory, induction by rupture of the fetal membranes. He reserves cesarean section for the complete type of placenta previa and stresses the need for blood bank centers in even the smallest population centers. Torpin is conservative in

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[4] **Cervicitis.** By Dr. Manuel Usandizaga, Catedrático de Obstetricia y Ginecologia, Jefe de Servicio de la Casa de Salud Valdecilla. Segunda Edición. 133 pages. Manuales de Medicina Practica. Salvat Editores, S. A., Barcelona-Buenos Aires, 1946.

[5] **A Treatise on Obstetric Labor.** By Richard Torpin, M.D., Professor and Chairman of the Department of Obstetrics and Gynecology, University of Georgia School of Medicine, Augusta, Georgia, 573 pages with 184 illustrations. Augusta Obstetrical & Gynecological Book Co., Augusta, Ga., 1948.

his treatment of heart lesions, preferring delivery from below. The chapter on cesarean section strongly emphasizes the reasons for the low incidence of cesarean section in this Georgia clinic.

This personal exposition on obstetric practice is directed toward those physicians and obstetricians who do the bulk of obstetrics in the United States. Torpin offers for them techniques which, for most conditions, can be used in the home. In this book they will find much valuable and practical information. PHILIP F. WILLIAMS.

The proceedings of the Conference of the Committee on Human Reproduction of the National Research Council, held in New York City in January, 1948, on **The Normal and Pathological Physiology of Pregnancy**[6] appear in bound form after earlier journal publication. This monograph is the sixth in a series on problems of reproduction. One conference session dealt with the subject of nutrition in pregnancy, in which Warkany discussed his recent experimental production of deformities. Darby and his co-workers demonstrated how the nutritional status during pregnancy could be assayed by biochemical methods, while Burke and Dieckmann discussed their clinical studies in the Lying-in Hospitals of Boston and Chicago, with observations and results somewhat dissimilar.

Four papers were devoted to the physiology of the toxemias of pregnancy. Page brought up to date recent research on placental dysfunction as an etiological factor. Munnell reviewed the subject of liver function in pregnancy, both normal and abnormal, while Kellogg, and Cosgrove and Chesley described certain findings in the toxemias, Kellogg from the standpoint of hemorrhagic lesions, and the latter authors more as to the clinical management.

Reynolds and his associates, in their paper on patterns of uterine contractility, give the results obtained by use of a multichannel tokodynamometer. With this method they have analyzed contractions in various types of inertia, regional retraction rings, nondilatation of the cervix, and false and normal labor. Their study shows reasons for various types of alterations in labor mechanisms, with suggestions as to how such alterations might be treated. Peters and his co-workers suggest the determination of serum iodine as a more appropriate measurement of infertility, habitual miscarriages, or the toxemias of pregnancy. This paper is interestingly correlated by the study of Delfs and Jones on endocrine patterns in abortion. Venning discusses the mode of excretion of hormone metabolites in normal pregnancy, and Dobriner and his associates discuss the excretion of ketosteroids in normal and abnormal pregnancies.

These are outstanding contributions on the physiology of pregnancy and represent the latest word regarding intensive investigation at present being pursued in many laboratories and clinics. Only slightly less important than the material presented in the papers are the excellent discussions by other investigators following each paper.

This monograph deserves reading and study by all who are interested in the problems of reproduction for although the material is on a high scientific level there is much of practical significance in this text. PHILIP F. WILLIAMS.

This book, **Maternity in Great Britain,**[7] presents the results of an inquiry into pregnancy and childbirth made in England in 1946, the basic material being 14,000 women who gave birth to a child in a certain specified week of that year. The inquiry was under the sponsorship of a joint committee of the Royal College of Obstetricians and Gynaecologists and the Population Investigation Committee.

Briefly, the investigation has attempted to answer the following questions: What services are available to women bearing children? How far are they used and what are

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[6] **The Normal and Pathological Physiology of Pregnancy, Proceedings of the Conference of the Committee on Human Reproduction of the National Research Council, on Behalf of the National Committee on Maternal Health, Held in New York City, January, 1948.** 176 pages with many illustrations and tables. The Williams & Wilkins Company, Baltimore, 1948.

[7] **Maternity in Great Britain, A Survey of Social and Economic Aspects of Pregnancy and Childbirth Undertaken by a Joint Committee of the Royal College of Obstetricians and Gynaecologists and the Population Investigation Committee.** 220 pages and 2 appendices. Geoffrey Cumberlege, Oxford University Press, London, New York, Toronto, 1948.

the factors affecting their use? Do they help women to regard childbirth as a normal process? How far do they prevent premature birth and infant death and promote the health of mothers and infants? Finally, what do parents spend on pregnancy and childbirth?

The method used in the inquiry seems to have been sufficiently broad to complete the aims and one can feel that the sample was adequate as to regions, frequency of births, housing, social classes (economic) and in relation to frequency of stillbirths and neonatal deaths. The subject matter of the text develops all of the general problems of maternity, antenatal care, care during confinement, relief of pain, and an extremely interesting chapter on the costs of childbearing.

In 1936, the English well-to-do apparently spent an average of $228 for the first baby, while manual workers' wives spent $144. Less money was spent for subsequent births, and poorer mothers economized progressively as their families grew in size. There was, of course, a marked difference among women who received care under municipal schemes. A section discusses the provisions of the National Health Service Act for free confinement care which has not removed many of the economic obstacles to childbearing in Great Britain.

Such special aspects of the maternity problem as prematurity are brought out. The conclusion is drawn that a reduction in prematurity should be expected from the improvement in the quality of the antenatal service rendered in Great Britain. As to the topic, "Infant Feeding," it is shown that 43 per cent of the inquiry mothers are wholly bottle feeding their babies at the end of the eighth week, and again the editors of the report feel that antenatal supervision stands out as a more important factor in the maintenance of lactation than any other factor. As to women in industry, it was found that most of the primigravidas employed in gainful occupations during pregnancy terminated their employment in mid-pregnancy and only a few, a small proportion of them, intended, at a date two months after the delivery, to resume such occupation. Home nursing received attention in the report. Illegitimately pregnant women suffered with respect to antenatal care; as to confinement care, it was about equal with others. In regard to economic circumstances these women were at a great disadvantage as compared to married women. Many became destitute and the assistance available to them in Great Britain was considered most inadequate.

The concluding chapter has many sound recommendations for the improvement of the faults brought out in the inquiry. It will be interesting to see a repetition of such an inquiry after the National Medical Service Act has been in operation for a few years.

For those who are interested in the social and economic aspects of pregnancy and childbearing, and all physicians should be interested, the book offers a great deal of value.

PHILIP F. WILLIAMS.

A three-volume **Obstetrics—Physiology, Pathology, Operations**[8] by Martius, assisted by Bickenbach, Nordmeyer, and the artist, Käthe Droysen, is the first important German contribution submitted to us since World War II. The publisher is the old firm of Georg Thieme, now in Stuttgart. I do not know why the ages and birthplaces of the authors are given—perhaps a military regulation; also the number of copies printed, 4,500. The object is to present a simple, noncontroversial exposition for students and physicians. The illustrations, in the main, are new.

[8] **Lehrbuch der Geburtschilfe.** von Prof. Dr. Med. Heinrich Martius, Direktor der Universitäts-Frauenklinik Göttingen. Unter Mitarbeit Von Professor Dr. Med. Werner Bickenbach; Professor Dr. Med. Kurt Nordmeyer; Käthe Droysen als Zeichnerin. Erster Teil: Physiologie, Unveränderter Neudruck. Mit 539, Zum Teil Farbigen Abbildungen. 568 pages. Zweiter Teil: Pathologie, Unveränderter Neudruck, Mit 486, Zum Teil Farbigen Abbildungen. 605 pages. Georg Thieme Stuttgart, 1948.

Die Geburtshilflichen Operationen. Ihre Ausführung und Anwendung. Ein Lehrbuch für Studierende und Gebrauchsbuch für Ärzte. von Prof. Dr. Med. Heinrich Martius, Direktor der Universitäts-Frauenklinik Göttingen. Sechste Auflage. Mit 281 Abbildungen. 287 pages. Georg Thieme. Stuttgart. 1948.

Volume I deals with normal situations. In view of the fact that 3 out of 1,000 women die in childbirth in Germany (4,500 in a year) and 5 per cent of children do so before or immediately after birth (75,000 yearly) he wants every practicing physician who does obstetrics to have at least four months of practical experience in an adequate maternity hospital. Practical advice is featured throughout.

The gross pelvic anatomy, the menstrual cycle, impregnation, early embryology, fetus, placenta, maternal pregnancy changes are adequately presented by Brickenbach. The illustrations are numerous, many in color, mostly schematic. A very elaborate exposition of the changes in the uterine muscle during pregnancy is presented, as well as other alterations in the maternal organism including such divergent subjects as chemistry of the blood, joint changes, and alterations in the adenohypophysis.

External and internal examination, pregnancy test, mensuration, determination of term, all profusely illustrated, are described. Under the subject of labor, the pelvis, the birth canal, the passenger, the forces at work, etc., are dealt with; finally, the course of a normal labor with digression in various directions. The conduct of labor by a midwife is next described, vaginal examination alone is indicated, median episiotomy recommended. The various normal positions are given in great detail, followed by multiple pregnancies. Nordmeyer is the author of the chapters on the puerperium and lactation and the physiology of the neonatus. This volume alone boasts of 539 illustrations.

Volume II contains the pathology, divided into four sections—disturbances of pregnancy, disturbances of labor, pathology of the puerperium, and the sick newborn. I have selected a few high spots for consideration. In threatened abortion the treatment with large doses of stilbestrol is not yet recommended. Emptying of the uterus is done in two stages by means of dilatation with laminaria for eight to twelve hours, next quinine and oxytocin, followed by curettage. Descriptions of extrauterine pregnancy, hydatid and chorionepithelioma with many colored illustrations are adequate. Much space is devoted to diseases of the pregnant woman. In eclampsia prophylaxis, Stroganoff treatment, venesection, and finally cesarean section are counseled. Malpositions, spontaneous and those due to pelvic or to fetal malformations or to malformations of uterus and vagina are described. In hospital practice, cesarean section is recommended for the uninfected patient with placenta previa. Penicillin apparently is just becoming available and is mentioned in the treatment of gonorrhea and as a possible means of combating puerperal sepsis.

Volume III corresponds to the sixth edition of Martius' book on obstetrical operations which first appeared in 1934. He not only emphasizes the dangers of the high forceps but believes that modern obstetrics would be improved by complete abandonment of this procedure. Classical cesarean has been abandoned universally. He describes the various suprasymphysial techniques. The book differs little from the earlier editions which have been received with much favor.

The three volumes form a comprehensive and adequate presentation of the subject. They are somewhat large and voluminous for the average student and even for the general practitioner but valuable for the specialist. R. T. FRANK.

The Third American Congress on Obstetrics and Gynecology was held in St. Louis in September, 1947. The previous meeting had taken place in 1942. A large number of organizations are members of this Congress. The Proceedings[9] cover everything minutely from invocation to the final manikin obstetric demonstration and the list of motion pictures which were shown, covering a total of 412 pages.

The contents covers the most diverse material, such as the advantages of the rooming-in unit in obstetric hospital; symptoms of sterility from every aspect; round-table dis-

[9]**Transactions of the Third American Congress on Obstetrics and Gynecology. Municipal Auditorium, St. Louis, Missouri, September 8 to 12, 1947.** Sponsored by the American Committee on Maternal Welfare, Inc. Edited by George W. Kosmak, M.D., and Robert N. Rutherford, M.D. 412 pages. Published by the Western Journal of Surgery Publishing Company, Portland, Oregon, 1948.

cussions (for example, asphyxia of newborn, prolonged labor, uterine myomas, early controlled ambulation, etiology of abortion, and Rh studies in 28,500 pregnant women). For the general meetings, such major subjects as follow were discussed in multiple presentations—anesthesia and analgesia; emotional aspects of pregnancy; cancer of cervix; cesarean section. The volume contains a fund of information and a valuable exchange of opinion in a free and unhampered forum. R. T. FRANK.

The text of **Obstetric Analgesia and Anesthesia,**[10] by Franklin F. Snyder, is divided into two sections, respiratory injuries of the child and the treatment of pain during labor. It discusses the present status of pain-relieving drugs from both an experimental standpoint and clinical use in obstetrics. The author states that obstetric analgesia is today the most widely discussed and the most controversial problem in obstetrics, and that the wide use of pain relief in labor has introduced a new factor, anesthetic drugs, into our consideration of the outcome of labor.

Dr. Snyder states that fetal respiratory injury is pre-eminent as a cause of death associated with birth. He points out the obvious fact that we must now add a measurement of this new pharmacologic factor influencing the fetus to our former regard only for the mechanism and the fetal environment. At present, the author suggests, the introduction of new methods of analysis permits the comparison of one agent with another in terms of the amount of respiratory depression in the fetus, and the degree of impairment produced in the labor mechanism. The application of such methods has facilitated the clinical trial of the drugs currently used in obstetric analgesia-anesthesia. They permit a determination of the margin of safety, not only for the mother but especially for the child, when we attempt to evaluate an agent in terms of potency of relief of pain, effect upon the fetus, and effect upon the labor mechanism.

In the discussion on respiratory injuries of the child, the author expands his ideas on the pharmacologic factors in labor, the mechanism of intrauterine respiration and the incidence of respiratory injuries before birth such as pneumonia, atelectasis, and asphyxia. He describes, in Chapter Seven, the laboratory methods by which the various agents may be assayed in regard to their effects upon both mother and fetus. By this assay the pharmacologic factor may be measured quantitatively in terms of depression of fetal respiration and impairment of the uterine expulsive mechanism.

In the section on treatment of pain during labor, the different agents are evaluated singly as to their potency, risk, and effect. The author discusses morphine, scopolamine, and the barbiturates in this regard, and proceeds to an evaluation of the rectal use of ether, alone or in combination of other agents and with certain synergistic drugs, and the rectal use of Avertin is discussed. He has analyzed the use and results of inhalation of ether and of chloroform and the narcotic gases, nitrous oxide, ethylene, and cyclopropane. The concluding chapter discusses the use of regional anesthesia in terms of physiology, technique, and the effects upon the mechanism of labor and on the fetus. Thus, we find caudal anesthesia, spinal, the different types of nerve block and local infiltration methods analyzed as to their risks, disadvantages, advantages, and effects.

The author, who has made outstanding contributions to the subject and study of fetal respiration, has ably compared studies in physiology of the fetus with the clinical results of the drugs now employed for relief of pain in labor. He has analyzed at length the pharmacologic factor introduced through the widespread efforts to promote analgesia. He has thoroughly reviewed the clinical reports available and has demonstrated how the effects of various agents can be assayed. Dr. Snyder presented a very fine study of a most important problem in the practice of obstetrics. PHILIP F. WILLIAMS.

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[10]**Obstetric Analgesia and Anesthesia, Their Effects Upon Labor and the Child.** By Franklin F. Snyder, M.D., Associate Professor of Obstetrics and Associate Professor of Anatomy, Harvard Medical School. 385 pages with 114 illustrations. W. B. Saunders Company, Philadelphia and London, 1949.

This comprehensive study of the **Control of Pain in Childbirth,**[11] by Lull and Hingson, appears in a third edition. The discussion of the drugs which may be used for this purpose includes the characteristics of each agent, an exposition of the pharmacologic action, a re-evaluation of the toxic effect of the drug, the technique of its use, the advantages, disadvantages and dangers, as well as the technique for the administration of each agent. The possible fetal complications resulting from the use of the various agents have also been described, and the drugs are evaluated from the standpoint of fetal salvage.

The book has been brought thoroughly up to date. Among the prominent revisions in this third edition is the considerably rewritten chapter on the anatomic considerations in regional nerve block, with special reference to caudal anesthesia. Another section which is new is devoted to the early care of the newborn infant, particularly in reference to the agent which may have been used in its delivery. There has also been added a discussion of the continuous caudal anesthesia study at Memphis, Tenn. The material there includes more than 5,000 continuous caudal, 2,500 saddle-block spinal and continuous spinal, and 800 births with general anesthesia. The statistical analysis of this group is compared with the results in the Philadelphia study. The figures and results are impressive and fully support the conclusions formed by the original study in the Marine Hospital on Staten Island.

Among other new material particularly is noted inclusion of the report from the Chicago Lying-in Hospital of spinal (saddle-block) anesthesia in obstetrics, with a full description of its use in 719 cases and the results as to pain relief, interference with labor mechanism, and the fetal respiratory processes. The present wide use of Demerol and scopolamine is well analyzed.

The book is almost encyclopedic in character, and although caudal anesthesia receives the largest degree of attention, every drug has been evaluated and there are many chapters of general interest, such as the one on psychology in pregnancy, in which the authors discuss and give their opinion of Reed's thesis on childbirth without fear, management of the puerperium, pain relief in home obstetrics, and the question of pain relief when maternal complications are present. The book is profusely illustrated and may be recommended as a practical working guide to all who are interested in pain relief in labor.

PHILIP F. WILLIAMS.

Many years of clinical experience and teaching have eminently fitted Miss Alice M. Hunt to write this book, **Anesthesia,**[12] which is primarily intended for the nursing profession. A reading of this volume should give nurses a clear and practical concept of the subject. After a brief, but interesting, historical review she stresses the dangers of the various agents used, and discusses the disadvantages as well as the benefits of premedication. She concludes that a proper choice of such drugs depends upon good judgment in relationship to the situation of each individual patient. Equally, she brings out the need for close care and watchfulness until the patient's return to the conscious state is completed.

Various agents, liquid, gaseous, Avertin, and those used intravenously or in local or regional anesthesia, are described as to their choice and action. Miss Hunt devotes considerable space to obstetric analgesia for the stage of dilatation, and analgesia and anesthesia for the stage of expulsion, both from the standpoint of relieving pain and from the standpoint of operative obstetrics. She feels it is unlikely that caudal anesthesia-analgesia for obstetrics will become routine. She suggests a trial of the psychological dissipation of the fear of labor as proposed by Reed. This fear, she states, creates increased tension in the opposing muscles of the corpus and of the cervix in labor, and the counteraction

[11] **Control of Pain in Childbirth.** By Clifford B. Lull, M.D., F.A.C.S., F.I.C.S., Director, Division of Obstetrics and Gynecology, Philadelphia Lying-In Unit, Pennsylvania Hospital, and Robert A. Hingson, M.D., F.I.C.S., F.A.C.A., F.I.C.A. Third Edition. 508 pages with 171 illustrations and 10 color plates. J. B. Lippincott Company, Philadelphia, London, Montreal, 1948.

[12] **Anesthesia: Principles and Practice, a Presentation for the Nursing Profession.** By Alice M. Hunt. 137 pages with 7 illustrations. G. P. Putnam's Sons, New York, 1949

is the origin of much parturient discomfort. She refers to the excellent results obtained at the New Haven Hospital and feels the method is deserving of a wide trial, at least in normal cases. The book closes with an excellent presentation on oxygen therapy to which, in a future edition, the author might well add some material on resuscitation.

The book is not only an excellent presentation for the nursing profession but offers as well an excellent and concise review of anesthesia for physicians.

PHILIP F. WILLIAMS.

This perennial and popular review of the obstetric and gynecologic literature of the world as selected by J. P. Greenhill, the 1948 Year Book,[13] comes to hand. There are 262 pages of abstracts on obstetrics and 322 pages of abstracts on gynecologic topics. An increasing number of references denotes an added widespread interest in the subjects of nutrition, the antibiotics in both specialties, and the influence of virus infections on the embryo. Twenty-five pages are devoted to abstracts on anesthesia-analgesia during labor. There is a recapitulation of Reed's methods. Greenhill continues to express his preference for infiltration techniques for obstetric surgery.

In the section on gynecology a very interesting discussion brings up the legal problems arising from the practice of artificial insemination, and it may well be read by those who use this method in the treatment of infertility. Quite a number of new operative procedures are described as well as a number of modifications of standard techniques. This part of the book is profusely illustrated. There are many references on the cytologic diagnosis of cancer, and 47 pages are filled with references to pelvic malignancy. The physiology of both subjects is full of new research.

As usual, Greenhill adds many personal notes in his editorial remarks. While not as sharply critical as in former years, the editor does not fail, however, to express vigorous dissent as he sees it. Once again, a list of questions is posed to test one's familiarity with the current literature.

PHILIP F. WILLIAMS.

Safeguarding Motherhood,[14] by Sol T. DeLee, is another manual for the expectant mother. Dr. DeLee has given an excellent discussion of pregnancy and parturition in language which should be easily understood by the average individual, and with enough development of the material on anatomy and physiology to satisfy the most curious. The subject of mental and physical hygiene includes a section on nutrition and the diet. The printed diets and the calorie tables should help a woman limit her weight gain during pregnancy. The minor disorders and the major complications of pregnancy are simply stated and the mechanism of labor and the use of some operative procedures are briefly described. Excellent directions are given for the puerperal hygiene and postpartum problems. Dr. DeLee discusses the return of menstruation and the various methods of birth control. The final chapter is practical advice on the normal newborn child and its care. Most of the questions that are usually asked by an expectant mother of her physician, Rh, early ambulation, rooming-in, determination of sex, calculation of date of delivery, signs of labor, suggestive symptoms of complications, are answered here. The book is well recommended as an aid in the instruction of an obstetric patient.

PHILIP F. WILLIAMS.

In this small book, **A Way to Natural Childbirth,**[15] Miss Heardman presents a detailed description of the methods by which the expectant woman may be trained to relax during

[13] **The 1948 Year Book of Obstetrics and Gynecology.** Edited by J. P. Greenhill, B.S., M.D., F.A.C.S., Professor of Gynecology, Cook County Graduate School of Medicine; Attending Gynecologist, Cook County Hospital; Attending Obstetrician and Gynecologist, Michael Reese Hospital. 584 pages with 110 illustrations. The Year Book Publishers, Inc., Chicago, 1949.

[14] **Safeguarding Motherhood.** By Sol T. DeLee, M.D., Clinical Instructor of Obstetrics and Gynecology, University of Illinois; Attending Obstetrician at the Chicago Maternity Center. 119 pages with 42 illustrations. J. B. Lippincott Company, Philadelphia, London, Montreal, 1949.

[15] **A Way to Natural Childbirth, A Manual for Physiotherapists and Parents-to-Be.** By Helen Heardman, Diploma Bedford Physical Training College, Chartered Physiotherapist (Teacher's Certificates). With 119 pages and 66 illustrations. The Williams & Wilkins Company, Baltimore, 1948.

parturition. She devotes some pages to an exposition of Reed's principles and then, in a well-illustrated text, describes and shows the calisthenic exercises which it is felt will help enable a woman to achieve a painless labor and a spontaneous delivery.

The material is presented for the benefit of obstetricians and physiotherapists who may wish to teach these methods to pregnant women, either singly in private practice, or in small ward classes in a hospital service. The method is so well illustrated that teachers should have no difficulty in explaining the exercises to pregnant women. There are also exercises which should be of help in the puerperium and a description of breast massage by the physiotherapist which it is felt may promote lactation and make breast feeding easier.

This book should be of value to those who wish to teach the physical phases of Reed's method. PHILIP F. WILLIAMS.

A book published in 1942 by Usandizaga on the **Pathology of the Pelvic Articulations During Pregnancy**[16] has arrived belatedly. It appeared simultaneously in Madrid, Barcelona, Buenos Aires. It takes up the anatomy of the joints, the alterations produced by pregnancy, including particularly the relations and consequent development of pain, particularly in the lumbosacral region. R. T. FRANK.

The **History of Obstetrics and Gynecology in Spain,**[17] by Usandizaga, professor of Obstetrics and Gynecology of the Faculty of Medicine of Zaragoza, was published in Santader in 1944. There are a number of histories of Spanish medicine, for example Chinchilla, 1941; Hernández-Morejón, 1942, and Garcia del Real which was published in 1934, but they do not consider sufficiently obstetrics and gynecology. The volume deals mainly with the early history, starting with the Romans and Saracens, the medieval and religious eras, featuring Francisco Lopez of Villalobos, who practiced somewhere between 1473 and 1542, and who had an excellent knowledge of gynecology and obstetrics, spoke of sterility due to poor semen, other sterilities due to uterine trouble, discusses abortion, mole, dystocia, menorrhagia and metrorrhagia, etc. The era of witch doctors, monsters, etc., follows. The pregnant woman and lactation; their importance in Spanish literature and church are taken up. Men were permitted to attend childbirth in about the 18th century, much later than in France. There is a very realistic series of sculptures of pregnancy with the womb in situ, now found in the medical college of Madrid, dating from the eighteenth century, ascribed to the supervision and dissections of Gimbernat. They compare very favorably with some of our most modern models. He records that the first cesarean in Spain was in 1753 and was performed for transverse position. In 1779, the first symphysiotomy was done in Spain. At that time perineal expression of the head was practiced. The history of the nineteenth century is added as an appendix. This book is most profusely illustrated with rare and uncommon pictures and also has a bibliography.
R. T. FRANK.

Pizon is the author of a monograph on **Obstetrical Radiodiagnosis**[18] as part of the series, "L'Expansion Scientifique Française." The subject is adequately covered in brief form, including visualization of the fetus after it has attained the length of 20 cm.; the recognition of fetal death; fetal malformations; afterbirth; the determination of age by bone; the recognition of age of fetus. He describes the pelvis, radiopelvimetry as well as radiocephalometry. A special chapter is devoted to the radiology of the placenta, the recognition of extrauterine pregnancy and of uterine rupture. There are a considerable bibliog-

[16] **Patología Gravídica de las Articulaciones Pelvianas.** By M. Usandizaga. Primera Edicion. 120 pages. Ediciones Morata, Madrid, Barcelona, Buenos Aires, 1946.

[17] **Historia de la Obstetricia y de la Ginecología en España.** By M. Usandizaga. Catedrático de Obstetricia y Ginecologia de la Facultad de Medicina de Zaragoza, Jafe de Servicio de la Casa de Salud Valdecilla. 361 pages. Santander, 1944.

[18] **Radiodiagnostic Obstétrical.** By Pierre Pizon, Ancien Assistant d'Electro-Radiologie des Hôpitaux de Paris. 161 pages. L'Expansion Scientifique Française, 1948.

raphy and fifteen excellent plates. While this monograph contains nothing new, it is an excellent exposition of the subject, particularly for those not especially interested in minute technical details. R. T. FRANK.

Pediatrics

Pregnancy wastage which takes an enormous toll of life has been fully discussed in this monograph on **Fetal and Neonatal Death,**[19] by Edith L. Potter and Fred L. Adair. After a full description of intrauterine life from fertilization to term, the authors give in detail the correct technique of a postmortem examination of the fetus, proposed by them because of the marked difference in brain and heart lesions of adult and fetal organs. The technique suggested should result in bringing pathological changes more exactly to the attention of the obstetrician. The authors, pointing out the difficulty of determining the cause of death in many fetuses, feel that undoubtedly lethal factors are inherent in the germ plasma in many instances. The etiology and types of malformations are discussed, as well as the other causes of fetal and neonatal death, such as anoxia, birth trauma, prematurity, toxemia, and infections. Reference is made to the influence of virus infection on death and malformations of the embryo. Anoxic deaths are regadred as only those in which the primary cause of death lies outside the fetus. Obstetricians may read with benefit the section on birth trauma. Prematurity, the authors state, should not be considered a cause of death in the stillborn fetus. Unless some pathologic condition is present the fetus should be born alive. The authors feel no evidence has been presented that toxemia of pregnancy affects an infant after delivery, and they point to pneumonia as the most common infection in the newborn infant, stressing the influence of prolonged labor in which the membranes have ruptured early. Special pathology of systems is developed at some length. There is a short but excellent section on erythroblastosis. The statistics of the Chicago Lying-in Hospital and of the National Office of Vital Statistics have been brought well up to date, and the definitions and classifications in present use are stated.

The tremendous reduction in the maternal mortality rate which occurred in the United States in recent years points to the likelihood that a thorough and painstaking analysis of every fetal or neonatal death in the manner which the authors describe would do much to promote a striking increase in fetal salvage. PHILIP F. WILLIAMS.

Dr. Ethel C. Dunham, who for many years was a consultant on prematurity for the Children's Bureau of the United States Government, has brought together a tremendous amount of material of both statistical and clinical value in this publication, **Premature Infants, a Manual for Physicians,**[20] issued by the Federal Security Agency. Since the loss of life following premature births accounts for one-half of infant deaths in the first month of life, the need for such an excellent presentation of the whole subject is clearly apparent.

The text, of nearly four hundred pages, is divided into two parts. The first part, which may be regarded as a source of information in regard to prematurity, deals with such general considerations as the definition of and the criteria for prematurity, the statistical material as to the incidence, and cause, and the prevention of premature birth, the death rates and the causes of death, as well as the growth and development of premature infants. This section provides an excellent background for the clinical material and suggestions for the general care of premature infants which form the second part of the book.

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[19] **Fetal and Neonatal Death, A Survey of the Incidence, Etiology, and Anatomic Manifestations of the Conditions Producing Death of the Fetus in Utero and the Infant in the Early Days of Life.** By Edith L. Potter, M.D., Ph.D., Associate Professor in the Department of Obstetrics and Gynecology, the University of Chicago, Pathologist at the Chicago Lying-in Hospital, and Fred L. Adair, M.D., Mary Campau Ryerson Professor Emeritus, the University of Chicago. 167 pages with 38 illustrations. The University of Chicago Press, Chicago, 1949.

[20] **Premature Infants, a Manual for Physicians.** Children's Bureau Publication No. 325. By Ethel C. Dunham, M.D. 341 pages with 31 illustrations. Federal Security Agency, Washington, 1948.

Here Dr. Dunham has described the physiologic handicaps of the premature infant with detailed information as to care in the neonatal period, as well as methods of overcoming the definite nutritional handicaps. The prevention and therapy of other lesions or diseases particularly affecting the premature infant are amply described, from a preventive as well as a therapeutic aspect.

The appendixes, nine in number, are of value not only from certain statistical viewpoints but also for the detailed discussions and specifications for incubators and methods of feeding. There are many well-reproduced photographs, drawings, schematic representations of normal and pathologic sections of the systems, and of developmental sequences.

The literature is profusely quoted. The documentation is thorough and there are extensive bibliographies following each section. The manual covers the subject widely. It is a reference book of excellent value, and the practical suggestions as to treatment make the book highly recommended for everyday use. PHILIP F. WILLIAMS.

The American Academy of Pediatrics in cooperation with the United States Public Health Service and the United States Children's Bureau has made a nationwide study of **Child Health Services and Pediatric Education.**[21] The book is divided into two parts. Part One brings out the high lights of the actual information gathered in relation to private practice, hospital facilities, and the services of community health agencies. The second part deals with an evaluation of pediatric education, an analysis of all of the medical schools in the United States and all of the hospitals approved for pediatric residencies. There is a tremendous amount of informative material in both divisions of the text.

The diversities and inadequacies of the medical service given to babies and children in the United States apparently depend on the availability of competent general practitioners who are in charge of three-fourths of the private care of such children. The report stresses the need for more clinical instruction in pediatrics of undergraduates and suggests financial aid in fellowships to train specialists and the promotion of graduate training for general practitioners. Indeed, the whole problem on how to make good medical care available and adequate for all children would seem to be answered by an early expansion of pediatric education in the medical school to the practicing physician.

In so far as the newborn is concerned, it is shown that births in hospitals have increased from 37 per cent of all babies in 1935 to 82 per cent in 1948. In metropolitan centers only one birth in twenty took place at home while in isolated rural counties more than 50 per cent were house confinements. Hospital delivery, in many instances, is considered deficient in respect to certain selected characteristics such as nurseries for full-term sick babies separated from well babies, the lack of a house staff to care for the newborn, the lack of an isolated formula preparation room, the lack of a practical nurse on continuous duty in the nursery, and the use of unsterilized milk for the newborn.

The report states that training of physicians in the care of the newborn is a cardinal duty of the medical school. Because of the possibility of cross infection if ward classes are permitted in nurseries and since the problem involves both the obstetric and pediatric departments, such teaching presents a difficult problem in undergraduate education. It is felt that instruction as to care of premature infants is far less effective than for normal newborns. In a large percentage of hospitals the pediatric department does not have control of the newborn service. The training of residents in the care of the newborn and premature infant is undoubtedly incomplete in many hospitals. There are twenty out of 178 hospitals approved for pediatric residents' training which provide no experience at all in the care of the newborn or premature.

The logical subsequent step to this statement of inadequacy is "What is going to be done about it?" and the institutions concerned in the report are already making recom-

[21] **Child Health Services and Pediatric Education.** Report of the Committee for the Study of Child Health Services, The American Academy of Pediatrics, with the cooperation of the United States Public Health Service and the United States Children's Bureau. 269 pages. The Commonwealth Fund, New York, Oxford University Press, London, 1949.

mendations based on all levels. There are few connected in any way with the care of child health service, practice, administration, or education who will not find much of interest in this report. PHILIP F. WILLIAMS.

In this psychological analysis of a child from birth to marriage, **Your Child's Mind and Body,**[22] Dr. Flanders Dunbar has given practical answers to the usual as well as the most infrequent emotional problems. Dr. Dunbar very effectively discusses the problems of the infant in relation to the functions of rest and nutrition. In both situations, she explains, the parent has a dual responsibility not only to understand his child, but also to help the child understand him and consequently to understand the outside world. In these respects the child's future is determined, she states, not so much by what you say but by the way you say it.

Her recital of the self-selection experiment of the diet by infants should reassure many anxious parents in regard to the food desires of their children. Dr. Dunbar describes play as an experiment, to be allowed as freely as possible without parental interference, to permit the child to acquire a sense of causes and consequences. In other words, to develop objectivity. In discussing psychopathic behavior she states that the best guard against having a problem child is coming to terms with yourself sufficiently to avoid being a problem child to yourself and to your neighbors. She discusses the relationship of marriage to the emotional situations of a child, and feels that parents insecurely united usually have insecure children.

There is an excellent chapter on the subject of training a child, obedience, punishment, and building a child's character. The author feels that the emotional patterns of six years are definitely present and accentuated at sixteen, and that "obedience" should be kept out of the child-parent relationship as far as possible. The psychologic bases of minor or major crimes are thoroughly explained. The author does not feel it is ever too late to begin training to correct such disorders.

The final chapter on the child nearing maturity deals with the problems of sex and contemplated marriage and describes for both child and parent the partial relinquishing of certain home and family ties for new personal relationships. At the end of the text, and in addition to an index, Dr. Dunbar has tabled the emotional problems as they occur between the ages of one month and seven years, so that the interested parent may follow one problem or another through the various periods of development.

This is an excellent manual for parents, and it is also a good book for the physician who is called on to guide parents through the field of child care. PHILIP F. WILLIAMS.

Endocrinology

The Hormones. Physiology, Chemistry and Applications,[23] edited jointly by Pincus and Thimann is a two-volume work of which Volume I now is at hand. It is an attempt to bring together "a comprehensive presentation at the research level." Experimentalism receives full emphasis; where possible, practical applications to biology and medicine are featured. Volume I contains the chemistry, the role of the hormones in other than mammals, and some aspects of animal physiology, treated by fourteen authors of whom eleven are American and one each Canadian, English, and Irish. Volume II will cover mammalian endocrinology with clinical application. Volume I deals mainly with chemical physiology. It is written by chemists and appeals mainly to the chemist though, in part, it is of interest to and understandable by the physician. Thimann in two chapters discusses plant

[22] **Your Child's Mind and Body, a Practical Guide for Parents.** By Flanders Dunbar, M.D. 292 pages. Random House, Inc., New York, 1949.

[23] **The Hormones. Physiology, Chemistry and Applications.** Edited by Gregory Pincus, Worcester Foundation for Experimental Biology, Shrewsbury, Mass., and Kenneth V. Thimann, Harvard University, Cambridge, Mass. Volume I. 886 pages. Academic Press, Inc., New York, 1948.

hormones, those of growth and others such as wound, flower-forming, and leaf-growth substances (Auxins and phytohormones, both those found in nature and the synthetic not so found).

Berta Scharrer deals with hormones in insects which play an important role in reproduction, postembryonic development, and production of hereditary characters (gene hormones). Whether insects secrete real sex hormones is controversial. A growth and differentiation hormone and a juvenile (inhibiting) hormone are recognized; also a number of organs which produce the hormones.

Frank A. Brown describes the hormones found in crustaceans. None of them has been obtained in a pure state. Parasitic castration modifies both male and female characters but no sex hormone has been demonstrated as such. An eyestalk hormone, not species specific, controls the melanophore action (sinus gland); also two from within the central nervous system (lightening and darkening hormones). Retinal pigment movement is likewise ascribed to hormonal control.

Greengard has written the chapter on "Hormones of the Gastrointestinal Tract." The four from the upper intestine—secretin, pancreozymin, cholecystokinin, and enterogastrone are best known. They have in common that no special cell group has been identified as their source, that their effect is limited to the organs of digestion, that their chemical make-up is unknown.

Roy O. Greep discusses the physiology and the chemistry of the parathyroid hormone. It is a well-rounded presentation, embracing physiology, relation to other glands, the hormone itself including preparation, effect on bone metabolism and clinical symptoms of over- and underproduction, its relation to pregnancy and lactation.

Jensen has written the chapter on the internal secretion of the pancreas. Crystalline insulin from various sources is identical and develops an effect of 24 I.U. per mg.

The next six chapters have an entirely different tone and aspect. They deal with the estrogenic, progestational, androgenic, and adrenal steroids which have been isolated, their structure determined, and many synthetically reproduced and active synthetic chemicals of similar action not occurring in nature which have been discovered. Dorfman, for example, who handles the biochemistry of the androgens, gives a list of 118 compounds. Pincus discusses assay of ovarian hormones, Pearlman the chemistry and metabolism of estrogen and those of progesterone as well. The chemistry and metabolism of the adrenal cortical hormones have been covered by R. D. H. Heard. These chapters are almost entirely theoretical chemistry with emphasis on chemical rather than biologic aspects and methods.

The chemistry of the anterior pituitary hormones has been written by Cho Hao Li and Herbert M. Evans. They recognize interstitial cell stimulating and lactogenic hormones, adrenocorticotrophic and growth hormones "isolated in pure form," the follicle-stimulating and thyrotrophic less purified. Whether their interpretation of purification should be accepted without reserve, I am not qualified to decide. These hormones certainly do not give clear-cut reactions on human beings as other pure products do.

The next chapter, that dealing with hormonal control of mammary growth (by Folley and Malpress of Reading, England), is of particular interest to me. Lured into endocrine research in 1906 by the spectacular report of Lane-Claypon and Starling on mammary growth induced by fetal, ovarian, and placental extracts, I spent an entire year of hard work only to discover that their aqueous extracts were inert and that their results were accidental and actually due to the ovarian cycle, which they had completely overlooked, mainly because they had neglected to use controls. "An Experimental Study of the Causes Which Produce the Growth of the Mammary Gland" (Arch. Int. Med. 7: 665, May, 1911). This erroneous work, which Starling never deigned to repudiate, still crops up perennially in the literature. Even today no exact clarification of the mammary cycle can be given. The estrogens, corpus luteum and adrenocortical as governed by the pituitary stimuli, produce growth but the placental influence, as described in minute detail by Halban in 1905, predominates. This classic, and in my opinion epochal paper, by the way, is not even mentioned by

the authors who, in keeping with the attitude shown throughout the volume, look askance at any observations not based upon experiments performed with *pure* substances!

The final chapter by the same two authors treats of the hormonal control of lactation by the prepituitary, adrenal, thyroid, and ovaries without real clarification.

This volume is a major contribution. It contains an immense amount of information, accessible through a good index. It collates and sifts scattered observations and presents them through the eyes of well-qualified specialists. The subjects dealt with are still in too labile a stage to allow us to consider this work as a definitive source book. R. T. FRANK.

Natural Products Related to Phenanthrene,[24] by Fieser and Fieser, is a third edition since 1936. Although a strictly chemical book issued as a monograph of the American Chemical Society, it is a source book indispensable to anyone doing steroid research, including research on the sex hormones, adrenal, etc. The authors emphasize that steriochemical configurations have been completely clarified. There is so much new material to be dealt with that several older sections have had to be omitted in spite of which the book has assumed double its previous proportions. They essay to systemize the bewildering steroid nomenclature.

The subjects dealt with are the quinones, morphine and related alkaloids; resin acids; sterols and bile acids; sex hormones; adrenal cortical hormones; steroid metabolism; cardiac active principles; steroid saponins, steroid and terpenoid alkaloids and stereochemistry (written by Richard B. Turner). Therefore, in spite of the mainly chemical aspects, much is of direct interest to the physician.

The authors mistakenly credit Aschheim and Zondek with the discovery that estrogenic material is present in the urine (Aschheim and Zondek, 1927). Actually the credit for discovering this most important source for obtaining purified female sex hormones belongs to Loewe and Lange in 1926. A great deal of information of interest in connection with endocrinology will be found within the pages of this important contribution. R. T. FRANK.

Clinical Endocrinology for Practitioners and Students,[25] by Martin and Hynes, is a short monograph which aims to limit itself to the well-authenticated requirements in endocrinology and to indicate the limitations of hormone therapy. It is a simple, well-arranged and well-planned description of the anatomy and physiology of the glands and includes the hormones secreted by them as well as their various effects. A special chapter is devoted to Fröhlich's syndrome and obesity. The various glands are taken up seriatim as are the breasts, and a chapter is devoted to hormonal implants. The exposition is short and accurate, more than a mere syllabus but too brief for a textbook. R. T. FRANK.

Essentials of Gynecologic Endocrinology,[26] by Riley, appears to be a student manual used at the University of Michigan Medical School. It is printed in offset but is very well carried out so that it is almost as easy to read as ordinary print. This is a well-arranged detailed lecture syllabus with some instructive graphs. The monograph is arranged in three sections—endocrine physiology, clinical and diagnostic procedures, sex-hormone chemistry and endocrine preparations. The laboratory descriptions are rather sketchy and the bibliography is somewhat haphazard. R. T. FRANK.

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[24] **Natural Products Related to Phenanthrene.** By Louis F. Fieser and Mary Fieser, Department of Chemistry, Harvard University. Third Edition of the monograph previously entitled "Chemistry of Natural Products Related to Phenanthrene," by L. F. Fieser. 704 pages. Reinhold Publishing Corporation, New York, 1949.

[25] **Clinical Endocrinology for Practitioners and Students.** By Laurence Martin, M.D. (Camb.), F.R.C.P. (Lond.), Physician to Addenbrooke's Hospital, Cambridge; and Martin Hynes, M.D. (Camb.), M.R.C.P. (Lond.), Reader in Medicine in the University of Cambridge. Foreword by Sir Lionel Whitby, C.V.O., M.C., M.D., F.R.C.P., D.P.H., Regius Professor of Physics, University of Cambridge. With 8 plates and 22 text-figures. 222 pages. The Blakiston Company, Philadelphia, Toronto.

[26] **Essentials of Gynecologic Endocrinology (With Sections on the Male).** By Garner M. Riley, Ph.D., Assistant Professor of Obstetrics and Gynecology, University of Michigan Medical School. 205 pages. Caduceus Press, Ann Arbor, Mich., 1948.

Miscellaneous

This book, **Clinical Aspects and Treatment of Surgical Infections,**[27] by Frank Lamont Meleney, is a systematic review of the surgical infections. It is based on the author's experience of more than twenty-five years as both a clinical surgeon and a practical as well as a research investigator of the pyogenic and necrotizing organisms found in surgical infections. Chapters in the book have been contributed by former associates of the author: Lockwood, Harvey, Longacre, and Sandusky. The last two have written on surgical infections in war wounds.

The book is truly a history of the treatment of surgical infections over the period of three decades. The author describes the treatment of these bacterial invasions before the advent of sulfonamides, during the time they were first introduced, and since the availability of penicillin, streptomycin, and bacitracin. The latter antibiotics were discovered in the author's laboratory. The volume is thoroughly documented, and an outstanding feature of the presentation is the use of illustrative cases covering the three distinct periods of therapy. One readily appreciates in studying these case reports the importance of the integration and positive correlation of a bacteriological laboratory with a surgical service.

Of especial interest is the discussion of surgical infections of the genital and urinary tracts, more especially pelvic and puerperal infections. It may be remembered that Dr. Meleney made a classic contribution to puerperal sepsis in presenting, some twenty years ago, the results of his epidemiologic and bacteriologic investigation of an epidemic of hemolytic streptococcus puerperal fever in a New York maternity hospital. His recommendations, made at that time from a prophylactic and preventive standpoint, have aided in diminishing or eliminating such outbreaks.

The volume is highly recommended. PHILIP F. WILLIAMS.

The authors feel that, in view of the great increase in the therapeutic use of blood and its derivatives, and the steady growth in the number of blood banks, there should be a text to cover the subject in its entirety. DeGowin, Hardin, and Alsever offer in this volume, **Blood Transfusion,**[28] a text for those whose patients receive transfusions, those who supervise the services, and those who perform the tests and necessary procedures. The first eight chapters are devoted, one might say, to clinical considerations. The remainder, and a much larger portion of the text, discusses the technical aspects.

Emphasis is laid on the various aspects of whole-blood transfusions because as clinicians the authors consider that whole blood is the major need in the treatment of patients, and that the great majority of patients who need blood require erythrocytes particularly. It is of interest that, in 1818, James Blundell, an English obstetrician, revived the procedure of transfusion and advocated its use in the treatment of acute obstetric hemorrhage. He insisted that human blood was more effective than that of animal origin, and his writings probably introduced the subject to the American profession.

After a short historical perspective, the therapeutic choice and the merits of products for use intravenously are discussed. In the section on the immunology of blood, the various

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[27] **Clinical Aspects and Treatment of Surgical Infections.** By Frank Lamont Meleney, M.D., F.A.C.S., Associate Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University; Associate Visiting Surgeon, Presbyterian Hospital, New York City. 782 pages with 282 illustrations. W. B. Saunders Company, Philadelphia and London, 1949.

[28] **Blood Transfusion.** By Elmer L. DeGowin, M.D., Associate Professor of Internal Medicine, State University of Iowa, Director, Blood Transfusion Service, University Hospitals, Member of the Committee on Blood and Blood Derivatives, National Research Council, Member of the Advisory Board for Health Services, American National Red Cross, Secretary of the Subcommittee on Blood Substitutes, National Research Council, 1940-1945; Robert C. Hardin, M.D., Assistant Professor of Internal Medicine, State University of Iowa. Formerly Senior Consultant in Blood Transfusion and Shock in the European Theater of Operations, U. S. Army, and Commanding Officer of the ETO Blood Bank; and John B. Alsever, M.D., Senior Surgeon, U. S. Public Health Service, Chief, Professional Standards, Hospital Division, U.S.P.H.S., Director of the Syracuse University Blood Transfusion Service, 1942-1944, Director of the Civilian Blood Donor Service and Associate National Medical Director, The American National Red Cross, 1944-1946. 565 pages, illustrated with 200 diagrammatic drawings. W. B. Saunders Company, Philadelphia and London, 1949.

groups, types and phenomena of agglutinations are described. Two chapters are devoted to the Rh-Hr blood types and isosensitization. The authors have attempted to simplify the veritable mosaic of antigens which are transmitted from parent to offspring by chromosomal combination. In the discussion of isosensitization and transfusion, the authors have fully developed the subject as it is seen in obstetric practice, and have given an excellent presentation of the many angles of this disturbing obstetrical problem. In the prevention of erythroblastosis fetalis no mention is made of the recently proposed use of hapten. This section might well be read by obstetricians, since practically every complication regarding the mother and fetus has been brought out, immunology, prognosis, diagnosis, and treatment. The collected studies from the literature on congenital malformations in erythroblastic infants suggest to the authors that isosensitization in the mother has some causal relationship to the fetus.

The succeeding four hundred pages of the book are devoted to laboratory procedures, the technique of transfusion of whole blood, the preparation and administration of plasma, of blood derivatives and of plasma substitutes. While this section is probably most useful to the physician who supervises transfusion services and to the laboratory technicians who perform the tests necessary, yet many sections, such as the discussion of transfusion complications in the recipient, transmission of disease, and possible accidents to the donors, merit attention by clinicians. The illustrations in this section, made by Ballantine, solve the problem of visual presentation of a difficult subject through a series of pictures on the margins of the pages, a series of flow diagrams which perfectly correlate and illustrate the text.

There is a good chapter on transfusion services, both in the operation of a hospital blood bank and the services in civilian practice in communities, regions, or states similar to wartime services. This particular part might well be read by those who look forward to a catastrophic calamity in civilian practice, or to a future atomic war. The final chapters, well illustrated, describe the necessary equipment and the preparation of apparatus and fluids for parenteral therapy.

A tremendous amount of material has been brought together in this book which is thoroughly documented and unusually well illustrated. Surely those who are concerned with blood transfusions or the use of blood substitutes should find much to help them in the problems of this mode of therapy. PHILIP F. WILLIAMS.

This monograph, **Shock and Allied Forms of Failure of the Circulation,**[29] by H. A. Davis, discusses exhaustively the various phases of the topic. Since acute failure of the circulation is met in practically every field of clinical practice, it follows that a book of this nature should be of great value in many lines. The logical arrangement of the contents carries the discussion from the author's excellent definition of shock and the various classifications which have been offered through the methods of diagnosis of shock, from trauma and hemorrhage, infections, failures of nutritional origin, and in individuals at the extremes of life.

The author gives an explanation of the origin of circulatory failure as well as an extended discussion of the physiological changes not only in the heart and vessels but in the various systems as well, and brings out very understandably the biochemical changes which are followed by the degeneration in organs and systems. There is an excellent discussion of irreversible shock.

Of particular interest to the readers of this JOURNAL should be the extended discussion on obstetrical shock. The author describes acute circulatory failure of obstetrical origin which may occur before, during, or after labor. He notes that better care and early detection have reduced the toxemia death rate and that better control of puerperal infections by

[29] **Shock and Allied Forms of Failure of the Circulation.** By H. A. Davis, M.D., C.M., F.A.C.S., Associate Professor of Surgery, Director, Division of Surgery, Graduate School of Medicine, College of Medical Evangelists, Los Angeles Division; Senior Attending Surgeon, Los Angeles County General Hospital and White Memorial Hopsital; Visiting Surgeon, Cedars of Lebanon Hospital and California Hospital. 576 pages with 55 illustrations. Grune & Stratton, New York, 1949.

the use of chemotherapeutic agents and antibiotics has made hemorrhage and shock the leading cause of maternal deaths. The subject is discussed from the clinical sense since obstetrical shock differs in no respect from that resulting from hemorrhage or trauma. The changes in circulatory physiology in pregnancy are discussed and followed by a description of the pathology and the factors, eleven in number, which the author states most frequently underlie the condition. The syndrome of concealed accidental hemorrhage is compared with the crush syndrome described during the blitz in Britain. The author feels that, although there are some similarities, further studies are needed to clarify this problem. There are also sections on shock in the fetus and the newborn, from trauma as well as other conditions.

Practically all agents currently used in anesthesia, the effects of preanesthetic agents, and the circulatory effects of curare are itemized in the chapter on circulatory failure from anesthesia. The author stresses the significance of anoxia in anesthesia in relation to circulatory failure. The constitutional factors in relation to pathogenesis are thoroughly taken up in the chapter entitled "The Circulatory Weakling." In this very interesting section, the problems of aging and of individualization as to operability are brought out. The final chapter discusses the treatment of shock and other forms of circulatory failure. Each section brings out very definitely and concisely the therapeutic measures which may be of value.

The volume is an outstanding presentation of the subject, and is highly recommended to the readers of this JOURNAL for the extended discussion relating to obstetrics and gynecology and the newborn.

PHILIP F. WILLIAMS

The sixth edition of Sir Arthur Keith's **Human Embryology and Morphology**[30] has now appeared. The first edition appeared in 1901, the fifth one in 1933. The present volume has grown to 690 pages with 578 figures. The introduction by the author is a mellow, broad-minded, and unpedantic review of the many changes in outlook, not only in embryology but in all branches of its allied sciences, which have taken place in the last forty-eight years. He states that he "still maintains that embryology becomes a profitable study only when we interpret its events in the light of evolution." This point of view predominates throughout the book. He emphasizes the profound changes in our point of view and knowledge derived from the discovery of the hormones, in embryology particularly as evocators and inductors. When the first edition was written, Germany formed the center of embryological and morphological research. This was soon transferred to the United States by the outstanding work of Franklin P. Mall and the development of the Department of Embryology of the Carnegie Institute of Washington. After Mall's death in 1917, the good work has been carried on by Streeter and now by Corner. A number of new chapters have been added by the division of old chapters, mainly those pertaining to the urogenital systems as well as those dealing with the development of the limbs, especially the growth and ossification of the human skeleton. In recent years the study of the earliest stages of the primate ovum development and the origin of the special embryonic structures and "presumptive areas" of the embryonic shield progressed. In this work, experimental embryology has by necessity been mainly confined to references. A tremendous amount of information has been tucked away in the chapter notes and references.

The book may, as heretofore, be considered a very standard, well-balanced, and detailed description of embryology. The presentation throughout is lucid and simple. It gives an impression of unhurried contemplation so often wanting in many modern books. As in other works on embryology, the origin of the ova, which to me has always held a peculiar fascination, is dealt with in a stepchild fashion. The author declares that the aberrant germ cells are no longer considered as a basis of teratomas. A very detailed index containing both subject and authors completes this very valuable textbook.

R. T. FRANK.

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[30]**Human Embryology and Morphology.** By Sir Arthur Keith. Sixth Edition (revised and enlarged). 690 pages. The Williams & Wilkins Company, Baltimore, 1948.

Current Therapy—1949,[31] which contains the latest approved methods of treatment for the practicing physician, is a large, 672-page volume arranged somewhat in encyclopedic fashion. The editor, Howard F. Conn, has enlisted twelve prominent physicians as consulting edtiors, and over two hundred contributors from various fields, who were selected mainly by these consultants. In addition, the editor apparently has had to act as pinch hitter in many instances because there are very few sections which do not contain articles from his pen. The book is written with the presumption that the diagnosis has been established. This enables the therapy to be presented in very short order. In many instances the methods recommended by several authors are given without prejudgment and presented in the alphabetical order of the authors' names. There are fourteen sections, each with its separate table of contents. In addition there is a good index of both subjects and authors.

For the purpose of review it is impossible to go into complete detail. I have reviewed it from the standpoint of a man who selects a number of subjects, upon the treatment of which he wants to inform himself. In the section on infectious diseases, the editor, Howard F. Conn, covers twenty-one of the forty subjects himself. It is impossible to judge just when the "books were closed." However, it may have been some months ago because there is no "specific remedy" for psittacosis or for typhoid. However aureomycin is mentioned for brucellosis. The next section is on the digestive tract. In the treatment of appendicitis, the methods of three surgeons are described. All important phases of the digestive system are gone into. Section 3 is on diseases of metabolism and nutrition. Section 4 deals with diseases of the endocrine system. In this, only a certain number of diseases have been selected for discussion. The fifth section covers the diseases of the urogenital tract, which is unusually complete. The venereal diseases are contained in Section 6. Three methods of treatment of syphilis in pregnancy are taken up. The succeeding section covers allergy. Section 8 pertains to the diseases of the skin and like the section on urology, is very complete. Diseases of the respiratory system are in Section 9. Section 10 contains diseases of the cardiovascular system; Section 11, those of the blood and spleen. Diseases of the nervous system are taken up in Section 12. In my mind there is a question whether the general practitioner will obtain much help on the rather elaborate therapy of brain tumors.

Section 13 is of particular interest to our readers as it covers obstetrics and gynecology in 53 pages. The section begins with antepartum care. In threatened abortion, I am surprised to find no mention of the high estrogenic therapy when the danger of interruption of early pregnancy appears likely. I cannot agree that "needling of the cul-de-sac for diagnosis by the general practitioner capable of minor surgery" would be a safe recommendation. There are two contrasting methods for treatment of the various forms of toxemia of pregnancy described. Cesarean section, analgesia and anesthesia in obstetrics, postpartum hemorrhage and postpartum care are taken up sequentially. The functional bleeding of endometrial hyperplasia is treated very cavalierly and could stand considerable expansion. Curettage, curettage and radium, and hysterectomy are mentioned without elaboration. The giving of estrogens in large doses for three or four days is likewise recommended, a length of treatment entirely inadequate, in my opinion. The paragraphs on female sterility are detailed and good. The treatment of bilateral cystic ovaries by surgery alone appears radical to me. Further on, menopause and vaginal infections are dealt with. I am surprised to find mammary substance still recommended as part of the medical treatment of fibroid tumors. Tumors of the ovary in the pregnant and nonpregnant women are described. I was somewhat shocked to find the statement that carcinoma of the cervix is more common in ward patients and carcinoma of the endometrium in private patients! For the treatment of carcinoma of the cervix, one author emphasizes radical operation; the other, the more current treatment by radiotherapy.

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[31] **Current Therapy—1949. Latest Approved Methods of Treatment for the Practicing Physician.** Howard F. Conn, M.D., Editor. Consulting Editors—M. Edward Davis, Vincent J. Derbes, Garfield G. Duncan, Hugh J. Jewett, William J. Kerr, Perrin H. Long, H. Houston Merritt, Paul A. O'Leary, Walter L. Palmer, Hobart A. Reinmann, Cyrus C. Sturgis, Robert H. Williams. 672 pages. W. B. Saunders Company, Philadelphia. 1949.

Carcinoma of the vulva is taken up and emphasis is placed on the early removal of precancerous lesions such as kraurosis and leucoplakia. Finally, in this chapter, pre- and postoperative care in gynecology is described. The final fourteenth section deals with physical and chemical agents, including burns, poisons, bites of insects and reptiles.

This very ambitious volume varies greatly in different sections. It certainly should prove of real use to pick up when confronted by conditions with which the physician is unfamiliar. It will perhaps lead him to the correct paths in further study of the situation.

R. T. FRANK.

The Pharmacologic Principles of Medical Practice,[32] by Krantz and Carr, is a textbook on pharmacology and therapeutics designed by the authors for medical students, physicians, and members of the professions allied to medicine. The average medical student will find the book a bit above his head. The arrangement is simple, consisting of nine parts. The introductory portion deals with the history of pharmacology, pharmacologic principles, and an introduction to drugs which includes the pharmacopoeia, prescriptions, methods of administration, and a description of the response of cells to drugs.

The subsequent parts include the anti-infective drugs, the response of the skin and mucous membranes, the response of the central nervous system to drugs. The latter include depressants such as alcohols, anesthetics, opium and its alkaloids, addictive analgesics and marihuana; the problems of drug addictions and then a description of the various depressants such as the barbiturates, etc., etc., as well as hypnotics and antipyretics; finally, the central nervous system stimulants.

Part V deals with the response of the autonomic nervous system covering both the stimulants and depressants of the sympathetic and parasympathetic system. Ganglionic depressants and response to histamine and antihistaminics are taken up. The next portion deals with the heart and circulation.

I read with particular care Part VII which covers the reproductive system. This deals with ergot and posterior pituitary for the uterus; gonadotropins, estrogen and progesterone, and androgens. The subject is well handled and well covered from the historical and the purely chemical, as well as the pharmacological and clinical sides.

Part VIII covers the effects of pharmacological agents on metabolism which includes water balance, renal threshold, carbohydrate metabolism in insulin, iodine metabolism, and, finally, calcium-phosphorus metabolism as affected by calciferol and the parathyroid hormone.

The chemical aspect is fully emphasized. Most chapters end with a chart of the official prescriptions and dosages and a short chapter bibliography confined largely to the most recent literature. A number of full-page photographs of well-known pharmacologists, both past and still present, adorn the volume. At the end there is a series of typical prescriptions covering various conditions.

R. T. FRANK.

Dr. Joseph H. Barach offers this book, **Diabetes and Its Treatment,**[33] to the general medical man as a clinical approach to an understanding of diabetes and its treatment. He states that there are more than one million potential diabetics in the United States, and that diabetes can be the most scientifically treated of all diseases. The control of the measurable factors in the disease requires, however, he states, knowledge and the total effort of the doctor, the nurse, a capable dietitian and most of all a cooperative patient.

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[32] **The Pharmacologic Principles of Medical Practice. A Textbook on Pharmacology and Therapeutics for Medical Students, Physicians, and the Members of the Professions Allied to Medicine.** By John C. Krantz, Jr., Professor of Pharmacology, School of Medicine, University of Maryland, Secretary of the General Committee of Revision of the United States Pharmacopoeia; and C. Jelleff Carr, Associate Professor of Pharmacology, School of Medicine, University of Maryland, Auxiliary Member of the Revision Committee of the United States Pharmacopoeia. 980 pages. The Williams & Wilkins Company, Baltimore, 1949.

[33] **Diabetes and Its Treatment.** By Joseph H. Barach, M.D., F.A.C.P., Associate Professor Medicine, University of Pittsburgh; Senior Medical Staff, Presbyterian Hospital; Chairman, Metabolism and Endocrinology Study Section, Research Grants Division, U. S. Public Health Service (1946-1951). 316 pages with 78 figures, many tables, and 317 diet schedules. Oxford University Press, New York, 1949.

The early portions of the book take up the history and a description of the disease and its background. The laboratory methods essential in diagnosis and treatment are set forth at length. A full discussion of the complications of this disease show the many pitfalls in its control, while an entire chapter is devoted to the circulatory complications.

Dr. Barach has given two excellent chapters on surgery in diabetes and on pregnancy in the diabetic. In the latter chapter he states that one out of six patients who are pregnant and diabetic has developed the disease during pregnancy. He contrasts the results obtained in the preinsulin and insulin regimes. He feels that cesarean section is the optimum method of delivery. White's principles in handling pregnancy in diabetics are elaborated upon, and schedules are presented for hormonal substitution therapies, diets during pregnancy, and detailed instructions for the last month of pregnancy, the prepartum or preoperative routine and postpartum care. He also discusses in this chapter the subjects of excessive insulin in the newborn and the care of the premature infant born of a diabetic mother.

The pharmacology of insulin in its various forms is described and the physiologic and therapeutic effects, as well as complications attendant upon its use, are taken up. The book is replete with detailed schedules of instructions for nurse, dietitian, and patient. Following a statement of nutrition in general and diet of the diabetic in particular, the author includes a section on diets, calorie values, diets for men under various categories, and for women and children. He gives a long list of emergency diets which may be suitable in complications, and there are many pages of recipes.

The complete discussion of this common and increasing disease, the excellence of the presentation, and the directions not only for the internist and his associates but also for surgeons, obstetricians, and public health officers, including the police, make this book a valuable contribution.

PHILIP F. WILLIAMS.

This book, **Successful Marriage,**[34] is an exceptionally fine presentation of the many problems of marriage and their proposed solutions. The editors, Drs. Fishbein and Burgess, chose thirty-eight outstanding and distinguished specialists to contribute chapters, and have arranged the material in the following broad divisions: preparation for marriage, the marriage, reproduction, the child in the family, and the social problems of sex and marriage. The division of the material and its assignment to its various contributors have been wisely made. We find in the first part a discussion of the selection of a husband or a wife, premarital sex relationships and the reasons for premarital and preconceptional examinations, and a chapter which answers most of the questions which the about-to-be-married couple may propose to the marriage counselor, be he psychologist, family physician, or gynecologist.

The second division, on the marriage, discusses frankly and in detail the sex aspects of the relationship, as well as the more practical personal and family problems of home management and finance. One also finds here a discussion of the various factors which produce marital maladjustments, and a discussion of miscarriages and abortions.

There are chapters on heredity and infertility, as well as the hygiene of pregnancy, and a description of labor in the third section of the book, and this part includes also a short statement on the prevention of conception and the commonly used methods, which are illustrated. The physical and mental growth of the child is well described, and there is an informative section on the subject of adoption, and another on the psychology of remarriage and the relationship of stepchildren in the family. Further growth of the child from the physical, sexual, and psychological aspects of development, and the preparation during adolescence for a successful marriage for the children in the family are included.

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[34] **Successful Marriage, an Authoritative Guide to Problems Related to Marriage From the Beginning of Sexual Attraction to Matrimony and the Successful Rearing of a Family.** Edited by Morris Fishbein, M.D., editor, *Journal of the American Medical Association* and *Hygeia, the Health Magazine;* and Ernest W. Burgess, Ph.D., Professor and Chairman, Department of Sociology, University of Chicago. 515 pages, illustrated. Doubleday & Company, Inc., Garden City, N. Y., 1948.

In the final part of the book, the changing attitudes on sex in our present social order are discussed, and are followed by statements as to prostitution and venereal disease. The incompatabilities of marriage and the divorce question are analyzed. The regression of the sexual life in men and women is dealt with in a discussion of the climacteric. The ability of women to take part in extramarital professional life, civic responsibilities, and other activities is clearly shown to be more than a working possibility. The place of the family in the community, the strength of individual family life, what the parents could and should give in the way of education, not only in family life, but also for their children's lifework, are well presented.

This book is full of accurate information, thoughtful discussion, and ably considered solutions of almost every problem of married life. It is written by men and women who are outstanding in their fields of endeavor. The book should be equally valuable on the desk of the family doctor, the marriage counselor, or the specialist or in the library of the homes of men and women who are eager to make of their marriage a secure and well-adjusted family unit in the community. PHILIP F. WILLIAMS.

Dr. Abner I. Weisman offers his opinion on what **The Engaged Couple Has a Right to Know**[35] in his guide to happy marriage. As Dr. Abraham Stone says in a foreword to the book, there have been rapid and forward social changes reflected in family relations in recent years. Young people who, in their new freedom, select their marital partners, have not only the opportunity for independent actions but also new ideas and responsibilities. To provide guidance and counsel, information and interpretation in these new responsibilities, Dr. Weisman presents a book to provide information and insight into the problems of engagement and early marriage. The physiology of youth and maturity is the basic theme of his early chapters on the motivating forces which lead to marriage. He utilizes the topics of anatomy and physiology, social implications of the engagement period, the physical health, and the premarital and preconceptional examinations, to emphasize the eugenic aspect of marriage. Again, the psychic side of the sex relation, the actual consummation of marriage, and the use of birth control are discussed in portraying the early days of a marriage. The successful consummation of marriage, pregnancy with psychic changes, and the arrival and reception into the home circle of the new baby, offer an opportunity for the author to advise on the frequent problems of the new triangular human relationship.

The volume in its easily understood presentation should serve to meet the needs of many for frank and skilled counsel in preparation for marriage. PHILIP F. WILLIAMS.

In his book, **Sex and You,**[36] Dr. LeMon Clark gives us a frank, easily understandable and well-presented discussion on the influence of sex in our lives. As to sex education, he feels that the average child has formed all of his basic attitudes by the time he is five years old, and that many of the incorrect attitudes and marital difficulties arise from a lack of truthful, honest explanations of sex in these almost infant years. Dr. Clark feels strongly that the social heritage of misinformation pursues an individual throughout life, and is the origin of many mistaken attitudes of later years. The discussion of the teen-age years of both boys and girls is excellent. Marriage relationship and customs are wisely examined while the subjects of pregnancy, infertility, and birth control are ably presented. The author's attitude toward divorce is broad-minded. The final chapter evaluates briefly some normal and distorted conventions and conditions, and the place of psychoanalysis in the frequent deviation of sexual relations.

[35] **The Engaged Couple Has a Right to Know.** By Abner I. Weiseman, M.D., Assistant Visiting Gynecologist and Obstetrician, Metropolitan Hospital; Associate Attending Gynecologist and Research Associate in Pathology, Jewish Memorial Hospital, New York, N. Y. 252 pages with 14 illustrations. Renbayle House, New York, 1948.

[36] **Sex and You.** By LeMon Clark, M.S., M.D. 205 pages. The Bobbs-Merrill Company, Indianapolis, New York. 1949.

The manner in which the book is written recommends it to the lay public and to those who are called upon to advise on the attitudes and functions of sex.

PHILIP F. WILLIAMS.

Education for Professional Responsibility[37] is a report of an interprofessions conference held in April, 1948. The conference was planned by leaders in education in schools of divinity, medicine, law, engineering, and business, since it had become increasingly clear to them that the major problems of professional education in these branches were common, and that unusual opportunities for fruitful discussion of such problems could be provided by a variety of experience of teachers in these different professions. The papers which constitute the formal portion of the conference are herewith published.

They deal with the objectives as well as the content and the method in such education. The changing concepts of objectives are historically developed, and it is interesting to follow the steps in professional education which now lead to a general acceptance of the case system in all five of the interested professions. Dr. James H. Means emphasizes this system in medical education in his discussion of the clinical clerkship which, he says, actually amounts to an apprenticeship. Dr. Means says that one of the problems of medical education is how to make the scholarly attitude persist through life, how to insure that the physician and surgeon will continue professional, not lapse into the merely vocational or commercial. Miss Eleanor Cockerill continues the subject of the conduct of medical education in discussing the relationship of social and environmental factors to medicine. A medical student, she feels, must be taught the relationship of these factors to medicine and must be helped to develop an ability to use this knowledge both in actual care of patients and in assuming a professional responsibility within society.

In the material presented in the final session on social and humanistic aspects of professional education these two factors are again referred to in connection with the problems of psychology and psychiatry. Dr. John Romano stresses that the trends and practices in current medical education may possibly develop in the medical student a one-sided, essentially physicochemical concept of human biology.

It would appear that many problems are common to these five professions and solutions by one branch of teaching may well be considered by the teachers in other lines. A reading of this small volume should make professional education in any branch more effective.

PHILIP F. WILLIAMS.

Just why a copy of the **Archives of Pathology**[38] from Lisbon arrived now when the number is dated December, 1941, I am unable to state. The number contains varia, has résumés in French, occasionally in German and English. There is an article on 439 cases of cancer of the cervix; another on isolation of the pertussis germ for diagnosis, in which 96 per cent of 167 cases gave positive reactions as they were encountered in the first week. The illustrations are excellent.

R. T. FRANK.

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[37] **Education for Professional Responsibility.** A report of the Proceedings of the Inter-Professions Conference on Education for Professional Responsibility held at Buck Hill Falls, Pa., April 12, 13, and 14, 1948. 203 pages. Carnegie Press, Carnegie Institute of Technology, Pittsburgh. 1948.

[38] **Arquivo de Patologia. Órgão do Instituto Português de Oncologia.** Vol. XIII, No. 3, December, 1941. F. Gentil e M. Athias, Palhavã, Lisboa.

Correspondence

Diethylstilbestrol Dosage in Threatened and Habitual Abortion and Premature Labor

To the Editor:

Dr. O. Watkins Smith's paper on "Diethylstilbestrol in the Prevention and Treatment of Complications of Pregnancy" (AM. J. OBST. & GYNEC. 56: 821, 1948) was read with a great deal of interest, especially the part about the dosage of stilbestrol. I have been trying for about ten years to find the correct dose of stilbestrol in threatened and habitual abortion and premature labor.

Most interesting to me were the following statements: (1) "15 cases [threatened abortion] on too high dosage, 4 of whom aborted." (2) "Of the 28 women who were given what we would consider an overdosage, only 17, or 61 per cent, carried." (3) "We have considered the dosage too high if 10 mg. or more are given daily for more than 10 consecutive days before the sixth week, 25 mg. or more daily before the tenth week, 50 mg. or more before the fifteenth week and 100 mg. or more before the twentieth week."

It has been found that the dose of stilbestrol varies in each individual. The amount of stilbestrol required is that amount that stops cramps, spotting, bleeding, and/or pain and keeps them from returning. The original dose may be from 25 to 1,000 mg. The dose required to keep these signs and symptoms from recurring is usually ⅛ grain (10 mg.) to 1½ grains (100 mg.) daily. Most patients require 25 to 50 mg. (⅜ to ¾ grains) every morning. We have been unable to make up a table of doses in these conditions, and we have tried to for years.

As soon as the patient begins to abort, regardless of the week of pregnancy, 10 to 25 mg. micronized stilbestrol tablets are given immediately and 4 25-mg. tablets are given every 15 minutes until all signs and symptoms have stopped. Then 2 25-mg. tablets three times a day and at bedtime for one week, one 25-mg. tablet three times a day and at bedtime for one week. Then 50 mg. every morning on rising. In 24 to 48 hours the patient comes to the office and 10 c.c. (25 mg. per c.c.) of micronized stilbestrol are given intramuscularly twice a week for four to six doses. This aids in saving more threatened abortion cases. Two hundred fifty milligrams of stilbestrol intramuscularly as soon as possible after a patient begins to abort are a very valuable adjunct in the treatment of threatened abortion. The dose is not increased as term is approached. Regardless of the dose we have been unable to cause any patient to abort or produce any sign or symptom of abortion with doses that are many times (even a thousand times) more than those advocated by Dr. Smith, given in her table of dosage. The daily dosage of 5 to 1,000 mg. at any stage of pregnancy did not produce any harm to the pregnancy, mother, baby, placenta, nor was any harm shown by repeated weekly complete laboratory studies. We have given pregnant patients very large amounts of stilbestrol during pregnancy up to 120,730 mg. without producing any signs or symptoms of an abortion.

It has been my observation that the larger the daily dose, the surer the patient will be to carry the baby to term and deliver a normal baby. Also it requires a much larger daily dose of stilbestrol as the number of abortions which had occurred rises. In one patient who had lost thirteen babies, it required 77,040 mg. during the entire pregnancy to hold the fourteenth baby. In an habitual aborter who had lost six babies, it required approximately 30,000 mg. to carry the baby to term.

In premature labor it has been found that it requires 200 or more mg. daily of micronized stilbestrol to keep patients from aborting if they begin to have labor pains. To prevent possible premature labor from occurring again, 50 mg. daily are given up to the eighth month.

In conclusion, the larger the daily dose of stilbestrol, the surer the patient will be to carry the pregnancy to term and have a normal baby. It is impossible to abort a woman with stilbestrol regardless of the daily initial dose of 500 mg. or total dose of 120,730 mg. during the entire pregnancy. No set table of dosage of stilbestrol has been found by me because the dose varies in each individual. The amount that does the job is the required dose.

KARL JOHN KARNAKY, M.D.

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HOUSTON, TEXAS
MAY 14, 1948

Items

International Congress on Obstetrics and Gynecology

The committee on Clinics of the International and Fourth American Congress on Obstetrics and Gynecology is composed of the following:

Canada	Dr. Edwin Robertson, Kingston, Ontario
New England	Dr. Duncan Reid, Boston, Mass.
Central Northeast	Dr. Nicholson J. Eastman, Baltimore, Md. (Seaboard cities, Washington to N. Y. inclusive)
	Dr. Clyde L. Randall, Buffalo, N. Y. (exclusive of New York and Washington, D. C.)
South	Dr. H. Hudnall Ware, Richmond, Va.
Midwest	Dr. John L. McKelvey, Minneapolis, Minn. (Minnesota, Wisconsin, and Iowa)
	Dr. John I. Brewer, Chicago, Ill. (Missouri, Indiana, Illinois, Ohio, and Michigan)
Central Northwest	Dr. Edward S. Taylor, Denver, Colo.
Southwest	Dr. Conrad Collins, New Orleans, La.
Pacific Coast	Dr. Charles E. McLennan, San Francisco, Calif.

The Committee on Clinics plans, by September 1, to have information on the current, up-to-date activities all over the United States and Canada, in order to direct men: (1) whose travel plans are flexible, to the leaders in a given field of endeavor; and (2) those whose travel plans are fixed, to activities along their respective routes of travel.

In addition, the Committee plans to have in its possession information on various medical centers planning special demonstrations, wet or dry clinics, and exhibitions of research. Such information will include both: (1) the time and place of such demonstrations or exhibitions and (2) the number of visiting physicians who can be accommodated at a given place and time.

Finally, the Committee on Clinics plans to have a sort of travel routing agency so that if any visiting physician sends a list of subjects he wishes to observe, we can route him, either before or after the Congress, by way of the best possible places for satisfying his desires.

Inquiries should be directed to Mr. Karl S. Richardson, 24 West Ohio Street, Chicago, Ill.

American Board of Obstetrics and Gynecology, Inc.

The annual meeting of the Board was held in Chicago, Ill., from May 8 to May 14, 1949, at which time 236 candidates were certified.

New Bulletins, incorporating changes made at the recent meeting, are now available for distribution upon application and give details of all new regulations.

The next scheduled examination (Part I), written examination and review of case histories, for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 3, 1950. Application may be made until Nov. 5, 1949. Application forms and Bulletins are sent upon request made to

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY,
1015 HIGHLAND BUILDING,
PITTSBURGH 6, PA.